Middlesex Hospital London, Cancer Research Laboratories

ARCHIVES

OF

THE MIDDLESEX HOSPITAL

VOLUME XXXIII.

Thirteenth Report

FROM THE

Cancer Research Laboratories

CONTENTS.

London
MACMILLAN AND CO., LIMITED
NEW YORK: THE MACMILLAN COMPANY
DECEMBER 1914

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OF

THE MIDDLESEX HOSPITAL

13th

Thirteenth Report

FROM THE

Cancer Research Laboratories

(BEING THE THIRTY-THIRD VOLUME OF THE ARCHIVES)

EDITED FOR THE CANCER INVESTIGATION COMMITTEE

BY

W. S. LAZARUS-BARLOW, M.D., F.R.C.P.,

DIRECTOR OF THE CANCER RESEARCH LABORATORIES; FORMERLY LECTURER ON GENERAL PATHOLOGY AT THE MIDDLESEX HOSPITAL AND PATHOLOGIST AND LECTURER ON PATHOLOGY AT THE WESTMINSTER HOSPITAL

London

MACMILLAN AND CO., LIMITED

NEW YORK: THE MACMILLAN COMPANY

December 1914

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(1913–1914).

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NOTICE.

In the following pages, excepting where an asterisk (*) is placed, or where the context makes it clear that such is not the case, EVERY DIAGNOSIS OF MALIGNANT DISEASE HAS BEEN MADE AS THE RESULT OF MICROSCOPICAL EXAMINATION.

W. S. L.-B.

REPORTS

FROM THE

CANCER RESEARCH LABORATORIES

TABULATED SYNOPSES OF THE POST-MORTEM EXAMINATIONS AND OPERATIONS IN CASES OF MALIGNANT DISEASE DURING THE YEAR 1913.

By THE DIRECTOR and his ASSISTANTS.

In the following tables are given the results of all cases of malignant disease, as determined by microscopical examination, which were investigated in the Cancer Research Laboratories during the year. The material was derived partly from the post-mortem room and partly from the operating theatre. In all, 163 cases of malignant disease (males 57, females 106) have been examined microscopically. All of the above were in-patients. The total number of admissions to the hospital as in-patients during 1913 was 5,766*; viz., 2,482 males and 3,284 females. In addition 11 males and 47 females with malignant disease were admitted to the electrical (out-patient) department for X-ray and Radium treatment. Histological examination was not made in these cases.

* These figures do not include 174 patients admitted to observation ward; there were 381 births.

Besides the cases that have been mentioned, certain patients were admitted (either to the general wards or to the special wards) in which the diagnosis was not made certain by histological examination. These are grouped in two classes according to the relative probability of accuracy in the diagnosis.

In the first group, the diagnosis was founded on naked-eye appearances or on touch, but the patients were either discharged unrelieved from the Hospital at their own request, or else left after palliative or exploratory operation (e.g., cases of gastrostomy, colotomy, &c.).

In the second group the diagnosis was made upon clinical grounds.

GROUP I.

Cases diagnosed as Malignant Disease on Evidence derived from the Naked-Eye Appearance and Touch.

Site.	1913.		
	Males.	Females.	Total.
Tongue	37	3	40
Floor of Mouth	6	1	7
Palate	8	0	8
Tonsil	5	1	6
Pharynx	1	3	4
Larynx	13	2	15
Jaw	3	2	5
Glands of Neck	7	4	11
Skin	6	8	14
Rodent	6	4	10
Lip	13	—	13
Cheek	3	3	6
Pinna of Ear	5	3	8
Abdominal Wall	1	5	6
Bone	10	11	21
Breast	2	115	117
Cervix-Uterus	20	72	72
Ovary	—	9	9
Vulva and Vagina	—	11	11
Penis	1	—	1
Prostate	7	—	7
Bladder	7	2	9
Rectum	23	27	50
Anus	1	1	2
Testis	1	—	1
Totals	166	287	453

GROUP II.

Cases diagnosed on Clinical Evidence.

Site.	1913. Males.	Females.	Total.
Thyroid	5	1	6
Peritoneum	1	3	4
Gall-bladder	—	1	1
Bile Ducts	2	-	2
Duodenum	—	1	1
Caecum	2		2
Ileum	5	1	6
Appendix	—	2	2
Colon	9	9	18
Stomach	40	29	69
Œsophagus	17	7	24
Kidney	1	1	2
Totals	82	55	137

TABLE I.—

—		Total.		11—15.		16—20.		21—25.		26—30.		31—35.		36—40.		41—45.	
		M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
CARCINOMA.																	
Lip	Squamous	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Jaw	Squamous	1	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—
Mouth	Squamous	1	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—
Pharynx	Squamous	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Tongue	Squamous	6	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—
Skin of Neck	Squamous	—	3	—	—	—	—	—	—	—	—	—	—	—	—	—	1 branchioma
Larynx...	Squamous	4	1	—	—	—	—	—	—	—	—	—	—	—	—	1	—
Œsophagus	Squamous	7	1	—	—	—	—	—	—	—	—	—	—	—	—	—	1
Stomach	Spheroidal	3	2	—	—	—	—	—	—	—	—	—	—	—	—	—	1 pylorus
	Columnar	1	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Pancreas	Spheroidal	1	1	—	—	—	—	—	—	—	—	—	—	1	—	—	—
Kidney	Cyst-adenoma	—	1	—	—	—	—	—	—	—	—	—	—	—	1	—	—
Bladder	Transitional	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Intestine	Columnar	7	2	—	—	—	—	—	—	—	—	—	—	—	1 cæcum	1 rectum	—
Breast	Spheroidal	—	11	—	—	—	—	—	—	—	—	—	1	—	1	—	3
	Columnar	—	4	—	—	—	—	—	—	—	—	—	1	—	—	—	1
Ovary	Cyst-adenoma	—	1	—	—	—	—	—	—	—	—	—	—	—	1	—	—
	Columnar	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Uterus...	Transitional	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Cervix	Squamous	—	4	—	—	—	—	—	—	—	—	—	—	—	—	—	2
	Columnar	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Vagina	Squamous	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
RODENT		—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
SARCOMA		1	3	—	—	—	—	—	—	—	—	—	1 glands of neck	—	—	—	—
ENDOTHELIOMA		2	9	—	—	1 pituitary	—	—	1 ilium	—	1 breast	—	—	—	—	—	1 breast
NATURE DOUBTFUL		7	6	—	—	—	—	—	1 mediastinum	—	—	—	—	—	—	1 neck	1 abdominal glands
NO EVIDENCE OF MALIGNANCY		—	2	—	—	—	—	—	—	—	—	—	—	—	1	—	—
		43	59														

Post-mortem Cases.

46—50.		51—55.		56—60.		61—65.		66—70.		71—75.		76—80.		81—85.		86—90.	
M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	2	—	1	—	2	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	2	—	—	—	—	—	—	—	—
—	—	1	1	—	—	1	—	1	—	—	—	—	—	—	—	—	—
2	—	2	—	1	—	1	—	1	—	—	—	—	—	—	—	—	—
—	—	—	—	1 cardiac	—	1 body	—	—	—	1	1 cardiac	—	—	—	—	—	—
1 pylorus	1 body	—	—	—	—	—	1 pylorus	—	—	—	—	—	—	—	—	—	—
—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—
1 rectum	—	1 rectum	—	—	—	2 sigmoid rectum	1 rectum	2 rectum	—	—	—	—	—	—	—	—	—
—	1	—	1	—	1	—	—	—	—	—	3	—	—	—	—	—	—
—	—	—	—	—	1	—	—	—	—	—	—	—	1	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	1		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	1	—	—	—		—	—	—	1	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	*1	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	—	—	—
—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	1 mediastinum	—	—	—	—	1 jaw	—	—	—	—	—	—	1 bladder	—	—	—	—
—	1 breast	—	2 breast [illegible]	—	1 neck	1 larynx	2 breast	—	—	—	—	—	—	—	—	—	—
2 cheek sacrum	1 liver	2 neck mouth	1 bladder	—	—	—	*2 bladder	—		1 prostrate	—	—	—		—	1	—
—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

* Also Squamous Vagina.

TABLE II.—

		Total. M.	Total. F.	11—15. and under. M.	11—15. and under. F.	16—20. M.	16—20. F.	21—25. M.	21—25. F.	26—30. M.	26—30. F.	31—35. M.	31—35. F.	36—40. M.	36—40. F.	41—45. M.	41—45. F.
CARCINOMA.																	
Lip	Squamous	3	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—
Tongue	Squamous	3	—	—	—	—	—	—	—	—	—	—	—	—	—	3	—
Palate	Squamous	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Ear	Squamous	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Skin	Squamous	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Glands in Neck ...	Squamous	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Breast	Squamous	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Columnar	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Spheroidal	—	21	—	—	—	—	—	—	—	—	—	1	—	2	—	5
Gall Bladder ...	Columnar	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Intestinal ...	Squamous	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Columnar	5	5	—	—	—	—	—	—	—	—	—	—	—	1 rectum	—	—
	Spheroidal	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Uro-genital System ...	Squamous	1	10	—	—	—	—	—	1 cervix	—	1 cervix	—	1 cervix	—	1 cervix	—	1 cervix
	Columnar	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	Cystadenoma	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
RODENT CANCER		1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
SARCOMA		—	3	—	—	—	1 jaw	—	—	—	—	—	—	—	1 glioma	—	1 breast
ENDOTHELIOMA		1	8	—	—	—	—	—	—	—	—	—	1 breast	—	1 breast	—	1 breast
DOUBTFUL		1	4	—	—	—	—	—	—	—	—	—	—	—	1 breast	—	1 uterus
		22	59														
NON-MALIGNANT		3	19	1	1	—	1	—	1	—	—	1	1	—	3	—	4
		25	78														

Operation Cases.

46—50.		51—55.		56—60.		61—65.		66—70.		71—75.		76—80.		81—85.		86—90.	
M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
—	—	—	—	—	—	1	—	—	—	1	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—
—	—	2 cheek	—	—	—	—	—	1 forehead	—	—	—	—	—	—	—	1 leg	—
—	—	1	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—
—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	1	—	3	—	3	—	5	—	1	—	—	—	—	—	—	—	—
—	—	—	—	—	1	—	—	—	1	—	—	—	—	—	—	—	—
—	1 anus	—	—	—		—	—	—	—	—	—	—	—	—	—	—	—
—	1 sigmoid	—	1 rectum	1 rectum	1 rectum	2 rectum	—	1 rectum	—	—	1 rectum	1 sigmoid	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	3 cervix	—	1 cervix	1 penis	1 vulva	—	—	—	—	—	—	—	—	—	—	—	
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	1 ovary	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	1 cheek	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	3 breast	—	1 cervix	1 prostrate	—	—	—	—	—	—	1 peritoneum	—	—	—	—	—	—
—	1 glands in neck	—	—	—	—	—	1 lymph gland	1 prostrate	·	—	—	—	—	—	—	—	—
—	1	1	1	—	1	—	1	—	1	—	—	—	—	—	—	—	—

TABLE III.

Synopses of Post-mortem Cases.

CARCINOMATA.

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i) Congenital abnormalities. (ii) General remarks.	(i) Date of admission. (ii) Date of death. (iii) Surgical operation, if any.
1	R.F. 192/13	M	99	Squamous cell carcinoma of lip.	Cervical and bronchial glands.	Old pleuritic adhesions. Small cyst of peritoneum (? parasitic).	(ii) Emaciation.	(i) 25 Sept. '13. (ii) 8 Nov. '13.
2	W.S. 131/13	M	29	Squamous cell carcinoma of superior maxilla cf. $\frac{130}{13}$, $\frac{153}{13}$	Pleura, lung.	Old pleuritic adhesions. "Nutmeg" liver.	(ii) Well nourished.	(i) 14 Jan. '13. (ii) 15 June '13. (iii) Removal of left superior maxilla.
3	T.B. 91/13	M	45	(?) Squamous cell carcinoma of floor of mouth	Cervical glands.	Tubercle.	(ii) Emaciation.	(i) 11 Jan. '13. (ii) 24 April '13.
4	H.C. 166/13	M	49	Squamous cell carcinoma of pharynx.	Submaxillary glands.	... ...	(ii) Well nourished.	(i) 2 Aug. '13. (ii) 21 Aug. '13
5	W.D. 152/13	M	41	Squamous cell carcinoma of tongue.	Neck skin. Larynx, thyroid.	Broncho-pneumonia.	(ii) Emaciated.	(i) 17 April '13. (ii) 10 July '13.
6	J.B. 92/13	M	58	Squamous cell carcinoma of tongue.	Cervical glands, sternum, pleura.	Tubercle.	(ii) Very emaciated.	(i) 29 Nov. '12. (ii) 30 April '13.
7	T.B. 194/13	M	58	Squamous cell carcinoma of tongue.	Cervical glands.	Pulmonary tubercle.	(ii) Emaciation.	(i) 20 June '13. (ii) 10 Nov. '13.
8	J.G. 201/13	M	61	Squamous cell carcinoma of tongue.	Supraclavicular glands.	.. ..	(ii) Emaciation.	(i) 27 June '13 (ii) 22 Nov. '13.

x

9	J.C. 19/13	M	69	Squamous cell carcinoma of tongue (keratinised and prickle cells).	Cervical glands, right and left side of neck.	Ulcerated passage from buccal cavity to exterior. Small sub-peritoneal fibroid of stomach. Extensive atheroma of aorta and chief branches.	(ii) Well nourished.	(i) 2 Oct. '12. (ii) 21 Jan. '13.
10	W.C. 170/13	M	70	Squamous cell carcinoma of tongue.	... ...	... ...	(ii) Much emaciation.	(i) 21 April '13. (ii) 1 Sept. '13.
11	W.S. 143/13	M	45	Squamous cell carcinoma of neck (prickle and keratinisation) (branchioma).	... ...	... ...	(ii) Hosp. p.m. 89.	(i) 13 May '13. (ii) 20 May '13.
12	E.S. 29/13	F	66	Squamous cell carcinoma of skin of neck.	Cervical glands.	Pulmonary tubercle.	(ii) Very emaciated.	(i) 3 Dec. '12. (ii) 10 Feb. '13.
13	T.W. 130/13	M	68	Squamous cell carcinoma of neck. *cf.* $\frac{131}{13}$, $\frac{153}{13}$	Cervical glands.	Old pleuritic adhesions.	(ii) Well nourished.	(i) 29 April '13. (ii) 12 June '13
14	J.S.G. 79/13	M	42	Squamous cell carcinoma of larynx.	Cervical glands.	Tubercle.	(ii) Very emaciated.	(i) 26 March '13. (ii) 9 April '13.
15	L.B. 42/13	F	51	Squamous cell carcinoma of larynx.	Cervical and mediastinal glands.	Right leg has been amputated at lower third of femur.	(ii) Well nourished.	(ii) 18 Feb. '13.
16	A.K. 111/13	M	52	Squamous cell carcinoma of larynx.	Cervical glands.	Broncho-pneumonia, pleurisy.	(i) "Horse-shoe" kidneys. (ii) Emaciation.	(i) 1 May '13. (ii) 23 May '13. (iii) Tracheotomy.
17	A.S. 1/13	M	63	Squamous cell carcinoma of larynx (chiefly prickle).	Cervical glands.	Consolidation of lower lobes of both lungs. *Aorta* atheromatous: close to origin of cœliac axis is a deep ulcer filled with granular material.	(ii) Some emaciation. Healthy tracheotomy wound.	(i) 27 Sept. '13. (ii) 2 Jan. '13. (iii) Tracheotomy.
18	W.N. 200/13	M	66	Squamous cell carcinoma of larynx.	Cervical glands.	Perforation of aortic valves. Right kidney, pelvis, and bladder dilated, containing uric acid sand.	(ii) Great emaciation.	(i) 27 Dec. '12. (ii) 21 Nov. '13.

TABLE III.—SYNOPSES OF POST-MORTEM CASES—*cont.*

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of secondary new growth.	Other morbid changes present.	(i) Congenital abnormalities. (ii) General remarks.	(i) Date of admission. (ii) Date of death. (iii) Surgical operation, if any.
19	J.P. 172/13	F	46	Squamous cell carcinoma of œsophagus.	... ...	... ...	(ii) Hosp. p.m. 144.	(i) 1 Sept. '13. (ii) 4 Sept. '13.
20	J.T. 73/13	M	48	Squamous cell carcinoma of œsophagus (middle third).	Cervical glands.	Septic pneumonia.	(ii) Very emaciated.	(i) 12 Oct. '12. (ii) 29 March '13. (iii) Gastrostomy.
21	D.C. 202/13	M	50	Squamous cell carcimona of œsophagus.	... ...	... ...	(ii) Emaciation.	(i) 27 Sept. '13. (ii) 23 Nov. '13.
22	W.F. 179/13	M	52	Squamous cell carcinoma of œsophagus.	Stomach, bronchial glands, portal glands, liver	... ...	(ii) Emaciation.	(i) 30 July '13. (ii) 25 Sept. '13.
23	F.B. 1 2/13	M	53	Squamous cell carcinoma of œsophagus.	Cervical glands.	Broncho-pneumonia.	(ii) Some emaciation.	(i) 4 March '13. (ii) 11 May '13.
24	J.L. 55/13	M	60	Squamous cell carcinoma of œsophagus.	Trachea, cervical, bronchial, portal and lumbar glands.	Old pleuritic adhesions.	(ii) Emaciated.	(i) 25 Jan. '13. (ii) 13 March '13.
25	H.B. 106/13	M	63	Squamous cell carcinoma of œsophagus (chiefly prickle and kerat).	Lymphatic glands, adrenal.	... ...	(ii) Emaciation.	(i) 9 April '13. (ii) 20 May '13. (iii) Gastrostomy.
26	T.W. 191/13	M	67	Squamous cell carcinoma of œsophagus (middle third).	Abdominal glands	... ...	(ii) Emaciation.	(i) 14 Oct. '13. (ii) 11 Nov. '13.

27	W.T. 54/13	M	60	Spheroidal cell carcinoma of stomach (cardiac end).	Omentum, pancreas, right adrenal, left adrenal, right lung, portal, mesenteric, lumbar, mediastinal, bronchial and cervical glands.	Pneumonic changes in upper and lower lobes of right lung.	(ii) Emaciation.	(i) 21 Dec. '12. (ii) 13 March '13.
28	T.C. 184/13.	M	73	Spheroidal cell carcinoma of stomach.	... ...	... ...	(ii) Hosp. p.m. 165.	(i) 19 Sept '13. (ii) 11 Oct. '13.
29	H.K. 20/13	F	73	Spheroidal cell carcinoma of stomach (cardiac end).	Œsophagus, liver, parietal pleura, rib, left cervical, bronchial, œsophageal, portal, lumbar, and iliac glands.	... ...	(i) Small uterus (no cervix), with pinhole opening at head of short conical vagina. (ii) Emaciation.	(i) 14 Jan. '13. (ii) 27 Jan. '13.
30	M.M. 185/13	F	50	Columnar cell carcinoma (becoming transitional) of body of stomach.	Portal glands.	Two small vegetations on mitral valve.	(ii) Emaciation.	(i) 29 Sept. '13. (ii) 14 Oct. 13.
31	H.R. 51/13	M	62	Spheroidal cell carcinoma of body of stomach	Abdominal glands.	... ...	(ii) Hosp. p.m. 33.	(i) 24 Feb. '13. (ii) 25 Feb. '13.
32	S.A.B 183/13	F	44	Spheroidal cell carcinoma of stomach (pyloric end).	Portal, mediastinal, and lumbar glands.	... ...	(ii) Emaciation.	(i) 16 Sept. '13. (ii) 12 Oct. '13.
33	H.G. 6/13	M	46	Columnar cell carcinoma of pyloric end of stomach.	Liver. Portal and lumbar glands.	Small cyst in thyroid. Peritonitis.	(ii) Well nourished.	(i) 24 Dec. '12. (ii) 13 Jan. '13.
34	M.B. 173/13	F	63	Columnar cell carcinoma of pyloric end of stomach.	Liver, spleen, ovary, small intestine, abdominal glands.	... ...	(ii) Emaciation.	(i) 1 July '13. (ii) 10 Sept. '13.
35	T.D. 76/13	M	36	Spheroidal cell carcinoma of pancreas.	Mediastinal glands.	Distended gall bladder.	(ii) Jaundiced emaciation.	(i) 2 April '13. (ii) 5 April '13.

Table III.—Synopses of Post-mortem Cases—*cont.*

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i) Congenital abnormalities. (ii) General remarks.	(i) Date of admission. (ii) Date of death. (iii) Surgical operation, if any.
36	M.B. 21/13	F	54	Spheroidal cell carcinoma of pancreas.	Liver, gall bladder, peritoneum, scar in anterior abdominal wall, parietal pleura, cervical, mediastinal, bronchial, portal, and lumbar glands.	... ...	(ii) Emaciation, jaundice.	(i) 7 Dec. '12. (ii) 27 Jan. '13. (iii) Laparotomy.
37	A.S. 165/13	F	37	Malignant cystadenoma (papilliferous) of kidney (R).	Liver, spleen, bronchial glands, peritoneum, abdominal glands, lung, pleura.	... ...	(ii) Much emaciation.	(i) 29 Jan. '13. (ii) 17 Aug. '13.
38	L.J. 171/13	F	68	Transitional cell carcinoma of bladder.	... ...	Gallstones.	(ii) Very emaciated.	(i) 13 Jan. '13. (ii) 3 Sept. '13.
39	J.B. 148/13.	F	39	Columnar cell carcinoma of cæcum. (?) Also spheroidal cell carcinoma of ileum.	... ...	Cæco-abdominal fistula. Dilatation of pelvis of both kidneys. Recent pleurisy.	(ii) Much emaciation.	(i) 19 Aug. '13. (ii) 7 Oct. '13.
40	G.B. 163/13	M	65	Columnar cell carcinoma of sigmoid.	Abdominal glands, liver.	... ...	(ii) Well nourished.	(i) 11 Aug. '13. (ii) 16 Aug. '13. (iii) Colotomy.
41	G.S. 188/13	M	43	Columnar cell carcinoma of rectum.	Ilium, bladder, liver, left lung, lumbar, portal, and bronchial glands.	... ...	(ii) Emaciation.	(i) 23 Sept. '13. (ii) 22 Oct. '13. (iii) Colostomy.
42	A.S. 2/13	M	47	Columnar cell carcinoma of rectum.	Ilium, liver, left kidney, iliac gland.	Old adhesions at each pulmonary apex. Ileo rectal fistula.	(ii) Well nourished. Healthy colostomy wound.	(i) 11 Sept. '13. (ii) 2 Jan. '13. (iii) Colostomy.

43	F.H. 24/13	M	54	Columnar cell carcinoma of rectum.	... ...	... ...	(ii) Very emaciated.	(i) 20 July '12. (ii) 3 Feb. '13.
44	J.H. 7/13	F	64	Columnar cell carcinoma of rectum extending to vagina.	Vagina.	Old adhesions, both pleura. Adenoma simple in left adrenal. Small cyst in broad ligament.	(ii) Well nourished.	(i) 16 March '12. (ii) 14 Jan. '13. (iii) Inguinal colostomy.
45	E.B. 207/13	M	64	Columnar cell carcinoma of rectum.	Pelvic tissue. Bladder.	Old tubercle.	(ii) Emaciation.	(i) 11 Nov. '13. (ii) 11 Dec. '13. (iii) Colotomy.
46	H.W. 62/13	M	67	Spheroidal cell carcinoma (transitional) of rectum.	... ...	Lobar-pneumonia.	(ii) Hosp. p.m. 37.	(i) 8 Feb. '13. (ii) 5 March '13.
47	J.C. 199/13	M	69	Columnar cell carcinoma of liver (secondary) (rectum).	... ...	... ...	(ii) Hosp. p.m. 184.	(i) 4 Nov. '13. (ii) 18 Nov. '13.
48	F.M. 198/13	F	34	Spheroidal cell carcinoma of breast.	Supra-clavicular, bronchial mediastinal glands, pleura, liver.	Spleen, weight 10½ oz.	(ii) Emaciation. Slight jaundice.	(i) 16 Oct. '13. (ii) 17 Nov. '13.
49	R.S. 72/13	F	38	Spheroidal cell carcinoma of both breasts.	Liver, ribs, lumbar vertebræ.	... ...	(ii) Very emaciated.	(i) 1 Jan. '11. (ii) 28 March '13.
50	E.B. 71/13	F	43	Spheroidal cell carcinoma of breast.	Cervical, mediastinal, bronchial glands.	... ...	(ii) Well nourished.	(i) 23 Jan. '13. (ii) 27 March '13.
51	A.A. 64/13	F	45	Spheroidal cell carcinoma of breast.	Bronchial glands, liver.	... ...	(ii) Well nourished.	(i) 17 Feb. '13. (ii) 24 March '13. (iii) Amputation of both breasts.
52	A.K. 145/13	F	45	Spheroidal cell carcinoma of breast (?endothelioma.)	Lymphatic glands, lung, liver, bile duct, peritoneum, jejunum.	... ...	(ii) No emaciation. Jaundice.	(i) 30 May '13. (ii) 2 July '13. (iii) Amputation of breast.

TABLE III.—SYNOPSES OF POST-MORTEM CASES—*cont.*

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i) Congenital abnormalities. (ii) General remarks.	(i) Date of admission. (ii) Date of death. (iii) Surgical operation, if any.
53	E.F. 167/13	F	50	Spheroidal cell carcinoma of left breast.	Right breast, right and left axillary glands, pancreas.	Old pleurisy and tubercle.	(ii) Emaciation.	(i) 22 July '13. (ii) 25 Aug. '13. (iii) Amputation of left breast.
54	A.B. 99/13	F	55	Spheroidal cell carcinoma of breast (probably perienthelioma).	Lung, bronchial glands, vertebræ.	... ...	(ii) Emaciation.	(i) 15 Oct. '12. (ii) 5 May '13.
55	S.D. 14/13	F	57	Spheroidal cell carcinoma of right and left breasts.	Numerous. Liver free from deposits.	Mitral stenosis.	(ii) Well nourished.	(i) 21 Oct. '12. (ii) 18th Jan. '13.
56	E.S. 112/13	F	71	Spheroidal cell carcinoma of breast.	... ...	Senile kidneys.	(ii) Well nourished.	(i) 30 March '12. (ii) 23 March '13. (iii) Amputation of right breast.
57	S.F. 189/13	F	72	Spheroidal cell carcinoma of right breast.	Axillary and portal glands, liver.	... ...	(i) Patent foramen ovale. (ii) Well nourished.	(i) 16 Dec. '12. (ii) 27 Oct. '13.
58	L.B. 180/13	F	73	Spheroidal cell carcinoma of left breast.	Right breast, lung, pleura, diaphragm, liver; axillary, cervical, bronchial, mediastinal, and portal glands.	Cystic thyroid.	(ii) Slight emaciation.	(i) 7 Aug. '13. (ii) 2 Oct. '13.
59	F.P. 119/13	F	33	Columnar cell carcinoma of breast.	Humerus, dorsal and lumbar vertebræ, iliac bone, ribs, clavicle and sacrum.	... ...	(ii) Emaciation.	(i) 27 July '11. (ii) 29 May '13. (iii) Amputation of left breast.

60	J.R. 151/13	F	44	Colloid columnar cell carcinoma of breast.	Liver, adrenal (left).	... ...	(ii) Well nourished. Slight jaundice.	(i) 17 June '13. (ii) 13 July '13. (iii) Amputation of breast.
61	A.B. 25/13	F	57	Columnar cell carcinoma of breast.	Mediastinal glands, sacrum, right femur.	... ...	(ii) Well nourished.	(i) 11 March '12. (ii) 4 Feb. '13.
62	M.C. 186/13	F	78	Villous (colloid) columnar carcinoma of breast.	Axillary glands.	Extensive atheroma of aorta and branches.	(ii) Well nourished.	(i) 14 Aug. '13. (ii) 16 Oct. '13.
63	E.R.C. 78/13	F	40	Papillif. cystadenoma of ovary.	Peritoneum, pleura, liver (peritoneum).	... ...	(ii) Emaciation.	(i) 16 Jan. '13. (ii) 6 April '13. (iii) Laparotomy.
64	E.H. 205/13	F	51	Columnar cell carcinoma of ovary.	Bladder, diaphragm, pleura.	Pleural effusion.	(ii) Slight emaciation.	(i) 24 Sept. '15. (ii) 30 Nov. '13.
65	M.G. 159/13	F	50	Transitional cell carcinoma of uterus.	Bladder, peritoneum, inferior vena cava, inguinal lumbar, mesenteric, portal, mediastinal, and lower cervical glands.	... ...	(ii) Emaciation.	(i) 28 March '13. (ii) 2 Aug. '13.
66	A.W. 75/13	F	42	Squamous cell carcinoma of cervix (malpighian type).	... ...	Vesico- and recto-vaginal fistula.	(ii) Very emaciated.	(i) 2 March '13. (ii) 4 April '13.
67	E.L. 178/13	F	43	Squamous cell carcinoma of cervix.	Sacral, lumbar, mesenteric glands, liver, peritoneum, diaphragm.	... ...	(ii) Well nourished.	(i) 17 Sept. '13. (ii) 22 Sept. '13.
68	J.E. 164/13	F	47	Squamous cell carcinoma of cervix.	... ...	Ulcer on posterior wall of stomach adherent to pancreas.	(ii) Emaciation.	(i) 3 June '12. (ii) 16 Aug. '13. (iii) Colostomy.

Table III.—Synopses of Post-mortem Cases—*cont.*

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i) Congenital abnormalities. (ii) General remarks.	(i) Date of admission. (ii) Date of death. (iii) Surgical operation, if any.
69	H. McL. 169/13	F	68	Squamous cell carcinoma of cervix.	Liver, abdominal glands.	... ...	(ii) Much emaciation.	(i) 24 May '13. (ii) 31 Aug. '13.
70	E.H. 121/13	F	65	Columnar cell carcinoma of cervix. Squamous cell carcinoma of vagina.	Lumbar glands (both). Right ovary (columnar cell carcinoma).	"Vegetation" on mitral valve. Atheroma on aortic valves; and aorta. Right pleurisy. Granular kidneys. Gall bladder removed.	(ii) Well nourished.	(i) 29 July '12. (ii) 1 June '13. (iii) Cholecystectomy.
71	M.W. 52/13	F	76	Squamous cell carcinoma of vagina.	Uterus, ovary, peritoneum, ilium, jejunum, liver, omentum, pleura and lumbar glands.	Pedunculated cyst from right bronchus. Union of 3 aortic valve cusps.	(ii) Emaciation.	(i) 12 Feb. '13. (ii) 28 Feb. '13.
72	E.M. 61/13	F	53	Rodent cancer of forehead, extending to bone and dura mater	... ...	Mitral stenosis.	(ii) Well nourished.	(i) 23 May '11. (ii) 15 March '13.

SARCOMATA.

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i) Congenital abnormalities. (ii) General remarks.	(i) Date of admission. (ii) Date of death. (iii) Surgical operation, if any.
1	L.T. 46/13	F	34	Lymphosarcoma glands of neck.	... ...	... ...	(ii) Hosp. p.m. 30.	(i) 12 Feb. '13. (ii) 19 Feb. '13.
2	A.S. 193/13	F	48	Lymphosarcoma mediastinum.	Supraclavicular glands	... ...	(ii) Well nourished.	(i) 16 Oct. '13. (ii) 10 Nov. '13.
3	T.B. 77/13	M	62	Spindle cell sarcoma (? sup. maxilla).	... ...	... ...	(ii) Emaciation	(i) 13 Mar. '13. (ii) 9 April '13
4	E.T. 27/13	F	79	Small round cell sarcoma of bladder.	... ...	General peritonitis.	(ii) Much emaciation.	(i) 17 Dec. '12. (ii) 6 Feb. '13.

ENDOTHELIOMATA.

1	C.B. 53/13	M	20	Endothelioma (?pituitary body).	Nasopharynx, base of skull; first dorsal vertebra, liver; cervical glands, visceral pleura.	Early atheroma.		(ii) Well nourished.	(i) 16 May '12. (ii) 7 March '13.
2	M.R. 177/13	F	25	Lymphatic enthelioma of ilium.	Lung, pleura.	Cyst in left adrenal.		(ii) Deep jaundice. Emaciation.	(i) 28 Aug. '13. (ii) 22 Sept. '13.
3	E.M. 144/13	F	30	Lymphatic enthelioma of breast.	Sacrum, dorsal vertebræ, rib.	Pleural effusion.		(ii) Well nourished.	(i) 7 Feb. '13. (ii) 1 July '13. (iii) Amputation of left breast.
4	A.G. 190/13	F	43	Lymphatic entheliòma of breast.	Cervical and abdominal glands, liver, lung, peritoneum, ovary.	… … …	… …	(ii) Slight emaciation.	(i) 22 Oct. '13. (ii) 31 Oct. '13.
5	E.S. 141/13	F	47	Lymphatic enthelioma of breast.	Left breast, skin, pancreas, colon, both adrenals, pleura, left ovary; thyroid, axillary, cervical, bronchial, portal, and lumbar glands.	… … …	… …	(ii) Well nourished.	(i) 18 March '13. (ii) 21 June '13. (iii) Amputation of right breast.
6	A.S. 181/13	F	53	Lymphatic perienthelioma of breast.	Sternum, rib, cervical, dorsal, lumbar, and sacral vertebræ; occipital bone.	… … …	… …	(i) Each kidney has 2 ureters, and 2 renal arteries and 2 renal veins; 2 ureters on each side open close together in usual positions. (ii) Well nourished.	(i) 8 April '13. (ii) 5 Oct. '13.

TABLE III.—SYNOPSES OF POST-MORTEM CASES—*cont.*

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i) Congenital abnormalities. (ii) General remarks.	(i) Date of admission. (ii) Date of death. (iii) Surgical operation, if any.
7	M.L. 28/13	F	55	Hæmal perithelioma (? primary site).	Cervical glands, pleural cavity, rib, meninges.	... ...	(ii) Well nourished.	(i) 20 Jan. '13. (ii) 7 Feb. '13.
8	S.H. 23/13	F	58	Lymphatic enthelioma glands of neck.	... ...	... ...	(ii) Emaciated.	(i) 9 Nov. '12. (ii) 2 Feb. '13.
9	O.S. 162/13	F	62	Lymphatic enthelioma of left breast.	Right breast, skin, lungs, pleura, trachea, thyroid; liver, kidneys, adrenals, spleen; brain, meninges; colon, cæcum, pelvic peritoneum; axillary, cervical, bronchial, and mediastinal glands.	... ...	(ii) Slight emaciation.	(i) 23 Dec. '12. (ii) 6 Aug. '13.
10	F.K. 126/13	F	64	Endothelioma of breast.	Liver; right axillary, and cervical glands both sides, portal, lumbar, and iliac glands.	Several gastric ulcers. 24 oz. of turbid fluid in right pleural cavity.	(ii) Great emaciation.	(i) 4 March '13. (ii) 3 June '13.
11	A.H. 156/13	M	65	Perienthelioma of larynx.	Cervical glands.	... ...	(ii) Emaciation.	(i) 3 May '13. (ii) 21 July '13.

DOUBTFUL.

1	C.T.A. 209/13	M	—	Doubtful	... ...	... ...	(ii) Hosp. p.m. 203. Inquest.	(i) 28 Dec. '13. (ii) 28 Dec. '13.
2	B.D. 86/13	F	21	Nature doubtful (? lymphosarcoma), mediastinum.	... ...	... ...	(ii) Thin.	(i) 10 March '13 (ii) 16 April '13.
3	K.B. 174/13	F	43	Malignant (nature doubtful). Possibly endothelioma from abdominal glands. Vagina extending to bladder.	Abdominal glands	Recent vegetation on mitral valve.	(ii) No emaciation.	(i) 6 Aug. '13. (ii) 12 Sept. '13.
4	J.B. 154/13	M	44	Malignant (nature doubtful), neck.	... ...	... ...	(ii) Well nourished.	(i) 22 April '13 (ii) 14 July '15. (iii) Amputation of left middle of femur.
5	J.S. 39/13.	M	50	Squamous (malpighian) carcinoma (? lymphatic perithelioma) of cheek.	... ...	... ...	(ii) Emaciation.	(i) 10 Jan. '12. (ii) 15 Feb. '13.
6	M.S. 5/13	F	50	Malignant (nature doubtful) small mixed cell sarcoma (? primary in liver).	Supra clavicular glands, mesenteric glands. Chylothorax. Chylous ascites.	... ...	(ii) Hosp. p.m. 8.	(ii) 5 Jan. '13. Received 10 Jan. '13.
7	J.P. 147/13	M	50	(?) Squamous cell carcinoma (? sarcoma) of sacrum.	Lumbar, abdominal, and pulmonary glands; kidney and liver.	... ...	(ii) Emaciation.	(i) 13 May '13. (ii) 5 July '13.
8	G.C. 158/13	F	53	Nature doubtful, bladder	... ...	Pyonephrosis.	(ii) Emaciation.	(i) 17 July '13. (ii) 29 July '13

Table III.—Synopses of Post-mortem Cases—*cont.*

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i) Congenital abnormalities. (ii) General remarks.	(i) Date of admission. (ii) Date of death. (iii) Surgical operation, if any.
9	C.C. 153/13	M	54	Malignant (nature doubtful), floor of mouth *cf.* $\frac{130}{13}$, $\frac{131}{13}$	Epiglottis, lungs, pleura, pericardium (? also liver).	Large spleen, 12 oz. Fibrolipoma in left kidney.	(ii) Well nourished.	(i) 17 June '13. (ii) 12 July '13.
10	J.F. 168/13	M	54	Nature doubtful (? malignant disease), neck.	... ...	... ...	(ii) No emaciation.	(i) 22 July '13. (ii) 28 Aug. '13.
11	J.B. 114/13	F	63	Nature doubtful (? lymphosarcoma).	... ...	... ...	(ii) Hosp. p.m. 92.	(i) 22 May '13. (ii) 24 May '13.
12	J.C. 56/13	M	65	Malignant disease of bladder (nature doubtful).	Iliac gland.	Old pleuritic adhesions.	(ii) Well nourished.	(i) 4 Feb. '13. (ii) 14 March '13.
13	S.F. 80/13	M	74	Malignant disease (? spheroidal cell carcinoma) of prostrate. (? Small round cell sarcoma).	Liver.	... ...	(ii) Much emaciation. Hosp. p.m.	(i) 24 Oct. '12. (ii) 12 April '13.

A CONTRIBUTION TO THE STUDY OF *IN VITRO* PLASMA CULTURES OF MOUSE CARCINOMA AND RAT SARCOMA.

By C. PRICE JONES and J. C. MOTTRAM.

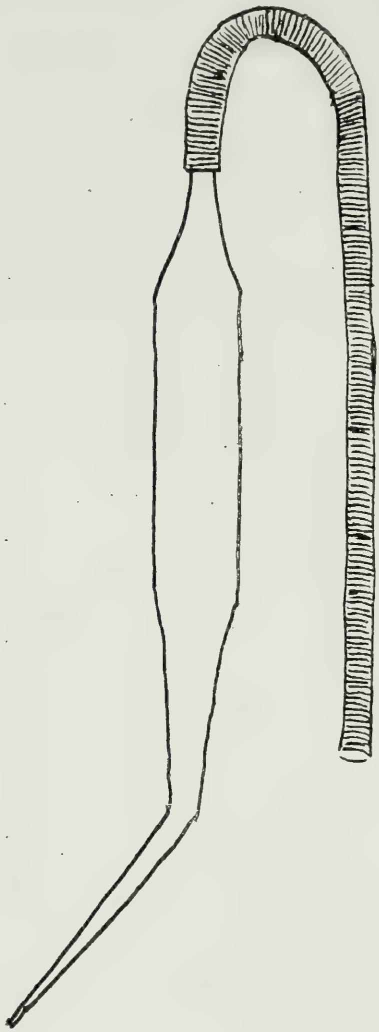
The object of this communication is to record some observations on plasma cultures of mouse carcinoma and of rat sarcoma.

Methods.—The methods adopted in this research were generally similar to those described by Carrel and other workers with *in vitro* cultures of tissues. In all cultures freshly prepared plasma was used.

After many trials of different ways for obtaining good and sufficient supplies of plasma, it was found most satisfactory to collect the blood from the abdominal vena cava, whereby much time was saved, and no dissection being necessary, there is less risk of tissue juice contamination. The animal was first anæsthetised with ether; the abdomen was then opened, and on turning aside the intestines to the left, and slightly raising the liver, the abdominal vena cava is well exposed. A sterilised paraffined glass pipette of about 5 cc. capacity, with a fine drawn out pointed nozzle, bent at an angle of about 145° (cf. Fig.), is introduced into the vein. The blood at once rushes up into the vessel; by adjusting a piece of fine rubber tubing to the end of the pipette, as much blood as is required can be sucked up; this arrangement is preferable to using a teat, as the pressure can be more easily controlled. For collecting blood from the mouse the pipette is smaller, and has a much finer nozzle than that used for collecting blood from the rat.

When a sufficient quantity of blood has been collected, it is blown out into a small sterilised and paraffined test tube, surrounded by ice, and as quickly as possible transferred to a centrifuge, and spun for about three minutes; the super-

natant plasma is then drawn up into small sterilised paraffined glass pipettes provided with capillary nozzles, which are then sealed in a flame, and kept in ice ready for use.



Pipette for use in preparation of plasma for *in vitro* cultures.

In the radium experiments, the portions of carcinoma and sarcoma, which were selected as far as possible from healthy, progressively growing tumours, were removed from the tumour-bearing animals a few hours before collecting the blood and before the preparation of the cultures, this interval depending on the length of time chosen for the exposure to radiation. The portions of tumour were placed on plaques of mica, and kept in the ice chest, or at room temperature, in sterilised Petri dishes containing a small quantity of sterilised Ringer solution to form a moist chamber.

In each observation two portions were taken, one being exposed to radium, the other (unexposed) being a control. In all cases the radium used was a 7 mgr. capsule, for a description of which see 12th Cancer Report, Middlesex Hospital, 1913, p. 21. The capsule was placed over the tissue and separated from it by a thin plaque of mica. Alpha rays were thereby excluded.

After the appointed interval, varying from $2\frac{1}{2}$ to 18 hours, the cultures were prepared in the usual manner on cover-

slips inverted over well slides, and sealed with paraffin; the cultures were then placed in a 37° C. incubator.

For permanent preparations, the specimens were fixed in Carnoy's fluid, and stained over night in dilute (1 in 100) Ehrlich's hæmatoxylin.

SERIES A.

Twelve cultures were made from portions of rat sarcoma which had been exposed to the 7 mgr. capsule for 2½ hours at room temperature.

Eight control cultures were made from portions of the same tumour which had not been radiated.

After 24 hours incubation, 9 of the radiated cultures showed extrusion of spindle cells, and 6 of these cultures were described as "excellent." Of the controls only 3 showed cell extrusion, 2 of these were "excellent."

One of the radiated cultures was fixed and stained; the nuclei of many cells were degenerated, either pyknotic or faintly stained, but in some the nuclei were healthy; there was no evidence of mitotic figures.

On the second day one radiated and one control culture were fixed and stained; both presented degenerated appearances, and there were no signs of mitotic processes.

On the fourth day most of the remaining cultures were fixed and stained; the degenerated appearances were very marked both in the radiated and non-radiated cultures, and in none was there evidence of mitosis; in the cultures multinucleated cells and cells containing fragmented nuclei were commonly met with.

In this series the radiated cultures showed more vigorous extension of cells than the control cultures. Degenerative changes appeared early and were noted in all the cultures. In the stained specimens there was no evidence of mitosis.

SERIES B.

Twelve cultures were made with normal rat plasma from portions of rat sarcoma which had been exposed to the 7 mgr. capsule for 3½ hours in the ice chest. Twelve cultures were made from portions of the same tumour which had not been radiated, but which were kept in the ice chest for 3½ hours.

After 24 hours incubation, 10 of the radiated cultures showed good extrusion of cells, and 4 cultures were described as "excellent"; of the non-radiated cultures, 8 showed extrusion of cells, but these were usually only few in number, and only one culture was described as "excellent."

On the second day 3 radiated cultures and one non-radiated were fixed and stained. In all cases many cells were degenerated and showed fragmented nuclei, but in none was there any evidence of mitosis.

On the third day 3 cultures in each set were degenerated or contaminated and were discarded, and the remaining cultures were fixed and stained. Of these, one of the non-radiated cultures showed 5 cells with mitotic figures; in all the others signs of mitosis were absent.

The radiated cultures showed more vigorous extrusion of cells than the control cultures. Degenerative changes appeared early. In the stained specimens there was no evidence of mitosis.

SERIES C.

Twelve cultures were made from portions of mouse carcinoma which had been exposed for $3\frac{1}{2}$ hours to the 7 mgr. capsule, at room temperature.

Twelve control cultures were made from portions of the same tumour which had not been radiated.

After 24 hours incubation, 3 of the radiated and 8 of the control cultures showed extrusion of spindle cells.

On the second day 8 radiated and 9 controls showed "growth."

On the third day 2 of each set of cultures were fixed and stained. In the radiated specimens there were spindle shaped and round cells, but no cells with mitotic figures, the nuclei in most cases being shrunken and degenerated. In the non-radiated cultures no cells with mitotic figures were observed, but the nuclei appeared healthy.

The remaining cultures were inoculated into mice with negative results in all cases.

In this series the radiated cultures did not show any more vigorous extrusion of cells than the control cultures.

Degenerative changes were not very pronounced on the third day. None of the stained specimens showed evidence of mitosis.

SERIES D.

Seventeen cultures were made in normal rat plasma from portions of rat sarcoma which had been exposed to the 7 mgr. capsule for four hours at room temperature, and 9 cultures were made from portions of the same tumour which had not been radiated.

After 24 hours, good extrusion of spindle cells was seen in 14 of the radiated and in 7 of the non-radiated cultures; the activity of the radiated cultures was certainly greater than that of the controls.

On the third day, after discarding 8 cultures which showed liquefaction, the remaining 18 cultures were washed in Ringer's solution for 50 minutes and then subcultured in fresh rat plasma.

After 24 hours incubation, 6 of the radiated and 3 of control cultures showed no "growth," but 2 radiated cultures were "excellent," and 5 others showed extrusion of spindle cells.

One of the "excellent" radiated cultures was fixed and stained, and showed one cell with an abnormal mitotic appearance, and another cell which was doubtful; the other "excellent" radiated cultures were stained on the following day and showed 2 cells with abnormal metaphase. One control culture was stained and showed 12 cells in mitosis.

After discarding liquefied and abortive specimens, 11 cultures were washed in Ringer's solution for 50 minutes and subcultured in fresh rat plasma.

After 24 hours incubation, 3 radiated and 2 control cultures showed cell extrusions, the remaining cultures were negative. Two days later the 5 positive cultures were fixed and stained. Of the radiated cultures, one was damaged in fixing, but showed great cell degeneration and no evidence of mitosis, and the other 2 cultures were also very degenerated and free from mitotic figures. Both the control cultures were good specimens, one showing 21 cells with mitotic figures, and the other which, owing to its thickness could only be partly examined, showed 8 cells with mitotic figures.

In this series the proportion of "takes" was good. The radiated cultures showed more vigorous extrusion of cells than the control cultures.

Signs of degeneration did not appear early in any marked degree.

Of the stained specimens, all subcultures, 2 out of 5 radiated cultures showed 2 cells with abnormal doubtful mitoses; 3 non-radiated specimens all showed cells in mitosis.

SERIES E.

Fourteen cultures were made from portions of mouse carcinoma which had been exposed for 4 hours to the 7 mgr. capsule, at room temperature.

Twelve control cultures were made from portions of the same tumour which had not been radiated.

After 24 hours, 4 radiated, and 3 control cultures showed extrusion of cells. One culture of each set was dried up and was discarded.

On the second day 7 (50 per cent.) of the radiated cultures showed good "growth," i.e., extrusion of numbers of cells; 9 (75 per cent.) of the controls also showed good growth. Of the radiated cultures, 5 were either dried or liquefied and were discarded, and one was fixed and stained; this specimen showed more or less degeneration of the cells and their nuclei, and there was no evidence of mitosis. Of the control cultures, 2 were discarded, and 1 was fixed and stained, and showed degeneration of the cells and absence of mitosis.

On the third day the 7 remaining radiated cultures and 8 of the 9 controls showed good extrusion of cells, but in all cultures the degenerative appearances were more marked. These cultures were then opened and received fresh plasma; in some cases the central mass was removed and subcultured, without washing.

On the fourth day only 3 of the radiated and 6 of the control cultures showed any fresh extrusion of cells, and the degen ration appearances were very marked.

On the sixth day 4 radiated and 6 control cultures showed cell extrusion.

On the ninth day 3 control cultures were fixed and stained, and all showed degenerated cells and absence of mitosis.

On the tenth day the radiated cultures again received fresh plasma, but all failed to "grow," saving one which was fixed and stained, and showed degenerated cells, often with fragmented nuclei, and in no case were there any signs of mitosis.

The remaining cultures failed to show fresh cell extrusion, and were finally discarded on the fourteenth day.

In this series 75 per cent. of the control cultures were good, and the radiated cultures did not exhibit any more vigorous extrusion of cells than the controls. Degenerative changes appeared early. None of the stained specimens showed mitosis.

SERIES F.

Twelve cultures were made from portions of mouse carcinoma, which had been exposed for 18 hours to the 7 mgr. capsule, in the ice chest.

Twelve control cultures were made from portions of the same tumour which had not been radiated, and were kept in the ice chest for 18 hours.

After 24 hours incubation at 37° C., 10 of the radiated cultures showed extrusion of cells, and in 2 cases there were large numbers of these cells, so that the cultures were noted as being "excellent."

Ten of the control cultures also showed "growth," and in one case the culture was marked "excellent."

On the second day degenerated changes were noticed in nearly every culture.

Later, a number of both sets of cultures were fixed and stained, and all showed much degeneration and no signs of mitosis.

All cultures were finally discarded on the eleventh day.

The radiated cultures showed rather more vigorous extrusion of cells than the controls. Degenerative changes appeared early. None of the stained specimens showed mitosis.

SERIES G.

Seven cultures were made from portions of rat sarcoma in immune rat plasma, 6 control cultures were made from the same tumour in normal rat plasma. After 24 hours incubation (2 cultures in each set were broken). 5 of the immune and 3 of the normal cultures showed cell extrusion.

On the fourth day 2 immune and 3 normal cultures were in healthy condition and were stained. In one of the immune cultures 18 cells showed mitotic figures, but in the other 2 the nuclei were degenerate and no mitosis was present. Of the 3 normal cultures, one showed 40 cells with mitotic figures, but in the other 2 cultures the nuclei were degenerated and fragmented, and no evidence of mitosis was noted.

In this series the proportion of "takes" is not very high. Of 5 stained specimens, 2 showed evidence of mitosis.

No especial difference is noticeable between the two sets of cultures.

SERIES H.

Twenty-four cultures of rat sarcoma were made, 8 with autogenous plasma, 8 with immune plasma, and 8 with normal rat plasma.

After 24 hours incubation, 6 autogenous cultures showed extrusion of cells, and 4 of these cultures were described as "excellent"; 6 immune cultures showed extrusion of cells, and 2 of these cultures were "excellent"; 5 normal cultures showed extrusion of cells, but in 4 only a few cells were extruded.

One culture from each set was fixed and stained; the autogenous culture showed no evidence of degeneration, and 5 cells with mitotic figures were noted; the immune culture showed no degeneration, and one cell in mitosis was noted; the normal culture showed only a few branched spindle cells, and no cells with mitotic figures were noted.

On the second day 2 autogenous, 1 immune, and 1 normal cultures were fixed and stained. One autogenous culture showed some degenerated cells, and one cell in mitosis; the other presented similar slight degeneration and 2 cells with mitotic figures. The immune culture showed very little degeneration, and 8 cells contained mitotic nuclei. The

normal culture showed marked degeneration in most nuclei, and no cells with mitotic figures were observed.

On the third day one of each set of cultures was fixed and stained. The autogenous culture appeared healthy, and 34 cells showed mitotic figures. The immune culture showed only round cells, some degenerated, and no signs of mitosis. The normal culture was much degenerated and no cells showed mitotic figures.

On the fourth day 2 autogenous, 1 immune, and 1 normal culture were fixed and stained. With the exception of one autogenous culture which showed one cell in telephase, the cells of all these cultures were more or less degenerated and no mitotic figures were to be seen.

From this series it appeared that better "growth" was obtained with the autogenous and immune plasma than with normal plasma; degenerative changes were more marked in the normal plasma cultures.

Of 14 stained specimens, 6 showed evidence of mitosis; of these, 5 were autogenous cultures, so that autogenous plasma appears to favour mitosis.

SERIES K.

Twenty-four double cultures of rat sarcoma and rat spleen were made with normal rat plasma; 12 being cultures of sarcoma and spleen of sarcoma-bearing rat, and 12 being cultures of the same sarcoma and spleen of immune rat. After 4 days incubation, all the cultures were discarded; 5 were fixed and stained; in one of these, 3 cells of spleen showed mitotic figures, but generally in all cases the cells presented much degenerative changes.

The series seemed to show markedly less activity than the cultures of sarcoma in the previous series. With two exceptions, the spleen never showed extrusion of spindle cells, but only large extrusions of small round cells.

No differences could be established between the two sets of cultures.

SERIES L.

Four sets of cultures were made:—

(1) Twelve cultures of rat sarcoma in normal rat plasma.

(2) Twelve cultures of rat sarcoma in normal rat plasma, with normal rat's spleen.

(3) Twelve cultures of rat sarcoma in normal rat plasma, and sarcoma-bearing rat's spleen.

(4) Six cultures of rat sarcoma in normal rat plasma, and immune rat's spleen.

On the second day 3 cultures of set (1), 7 of set (2), 10 of set (3), and 6 of set (4) showed extrusion of spindle cells.

On the fourth and fifth days 10 cultures were stained, and the remainder were discarded. Of the stained specimens, 1 culture of set (2) showed 48 cells with mitotic figures; the other cultures showed no signs of mitosis, the cells were degenerated, and the nuclei fragmented.

In this series the proportion of good growth is not high, only 26 out of 42 cultures.

No conclusions can be drawn respecting the slight differences observed between these 4 sets of cultures.

SERIES M.

Twenty-five cultures were made of rat sarcoma in normal rat plasma.

After 24 hours incubation, 23 of the cultures showed extrusion of spindle cells, and 10 were described as "excellent." Two were dry and discarded.

On the second day 4 cultures were found contaminated and were discarded. The remainder were washed in sterilised Ringer's solution for 50 minutes, and then subcultured in fresh plasma.

On the fifth day, after discarding damaged cultures, 19 subcultures were made.

On the sixth day one of the subcultures was fixed and stained; it was healthy in appearance, and 53 cells with mitotic figures were counted.

On the eighth day 3 cultures were fixed and stained; one was contaminated and degenerated and no mitotic figures were seen; one was largely degenerated and composed of round cells and a large ring of liquefaction, and one cell with a mitotic figure was noted; the third culture was less degenerated and showed 44 cells with mitotic figures.

The proportion of "takes" is very high (86 per cent). Degenerative changes occurred early. Of 4 stained specimens, all subcultures, 3 showed evidence of mitotis.

SUMMARY.

From the foregoing observations it is possible to draw the following conclusions:—

1. That in the plasma cultures of mouse carcinoma and rat sarcoma there is much irregularity in the proportion of "takes" (compare series G and L with series E and M), so that the number of growing cultures obtainable in any series is an uncertain quantity.

2. There is much variation in the date of appearance and degree of degeneration, both in the cultures of different series, and in the different cultures of the same series (cf. series A, B, E, and F, with C, D, and H).

3. That in the whole series of cultures, mitosis was not invariably present. Out of a total of 88 stained specimens, mitosis was observed in 18 (or in 20 if the 2 abnormal radiated specimens be included). Of these 88 stained specimens, 25 were radiated cultures, in which mitosis, with 2 possible exceptions, was never seen, and 14 specimens were cultures of carcinoma in which mitosis was never observed (it is probable however, that if these carcinoma cultures had been washed and subcultured some evidence of mitosis would have been present, since mitosis in carcinoma cultures had been observed by other workers), so that in 47 stained cultures of rat sarcoma, mitosis occurred in 18 specimens (about 39 per cent.); of these 18, 6 were subcultures, and since only 7 subcultures were stained, nearly 85 per cent. of subcultured specimens showed mitosis. In other words washing and subculturing favours mitosis, and it is to be regretted in this connection that more radiated cultures were not subcultured.

4. Radiation with 7 mgr. radium for $2\frac{1}{2}$ to 18 hours appears to have no retarding influence on the extrusion of cells; on the contrary, the radiated cultures were frequently observed to be more vigorous in this respect than the control culture (cf. series A, B, and F).

5. Finally, it appears that "growth" of *in vitro* cultures consists of two processes; (*a*) a spreading of area of the

Table I.

Tabular Statement of Experiments in Series A – M.

No.	Tissue.	7 mgr. Ra.				Not radiated.		Primary cultures (stained).				Subcultures (stained).				No. of mitoses.	
		Temperature.	Time.	Cultures.	Takes.	Cultures.	Takes.	Radiated.	Mitoses.	Not radiated.	Mitoses.	Radiated.	Mitoses.	Not radiated.	Mitoses.	Radiated.	Not radiated.
A	Rat sarcoma	room	2½ hrs.	12	9	8	3	6	0	2	0	—	—	—	—	0	0
B	,,	ice	3½ hrs.	12	10	12	8	8	0	6	1	—	—	—	—	0	5
C	Mouse carcinoma	room	3½ hrs.	12	8	12	9	2	0	2	0	—	—	—	—	0	0
D	Rat sarcoma	,,	4 hrs.	17	11	9	7	0	0	0	0	5	2?	3	3	3?	41
E	Mouse carcinoma	,,	4 hrs.	14	7	12	9	2	0	5	0	—	—	—	—	0	0
F	,,	ice	18 hrs	12	10	12	10	2	0	7	0	—	—	—	—	0	0
G	Rat sarcoma	—	—	—	—	13	8	—	—	5	2	—	—	—	—	—	58
H	,,	—	—	—	—	21	17	—	—	14	7	—	—	—	—	—	54
K	,, + Spleen	—	—	—	—	21	15	—	—	5	1	—	—	—	—	—	3
L	,,	—	—	—	—	42	26	—	—	10	1	—	—	—	—	—	48
M	Rat sarcoma	—	—	—	—	25	23	—	—	—	—	—	—	4	3	—	98
	Total ...	...	...	79	58	193	135	20	0	56	12	5	2?	7	6	3?	307
				73·4 per cent.		69·9 per cent.											

original mass by the extrusion of cells possessing long, often branched, amoeboid processes; (*b*) a division of cells by mitosis; and that "spreading" may occur quite independently of mitosis.

And whereas radiation with a 7 mgr. capsule of radium bromide for periods of time ranging from $2\frac{1}{2}$ to 18 hours has no retarding influence on the "spreading growth," it has a marked inhibiting effect on mitosis.

It would seem, therefore, that an increase in superficial area observed in an *in vitro* culture must not necessarily be regarded as growth in the sense of a multiplication of cells by mitosis.

Table II.

Summary of Table I. in respect of "Takes" and Mitoses.

	"Takes."	
	Radiated.	Non-radiated.
Mouse carcinoma (74 cultures)	66 per cent.	78 per cent.
Rat sarcoma (198 cultures)	80 ,,	68 ,,

	Mitoses.	
	Radiated.	Non-radiated.
Mouse carcinoma (20 cultures stained)... ...	0 ?	0 ?
Rat sarcoma (68 cultures stained)	3 ?	307

COMPARATIVE OBSERVATIONS ON CHANGES IN COLUMNAR AND IN SQUAMOUS EPITHELIUM, AND IN SUB-EPITHELIAL TISSUES, INDUCED BY THE GAMMA RAYS OF RADIUM.

By W. S. LAZARUS-BARLOW.

The experiments described below were carried out in the normal rat, and the region selected was the lower end of the rectum, together with the adjoining portion of the under-surface of the tail. It was desired to determine what differences, if any, obtain in the mode of response of the different varieties of epithelial cell when exposed to a definite amount of radium radiation. At the same time it was possible to make observations upon the sub-epithelial connective tissue and upon the muscular bundles lying yet more deeply.

Apart from the difference in character of the epithelium, the regions investigated differed in other respects. Thus the sub-columnar (sub-mucous) tissue is looser in composition than the sub-squamous (sub-cutaneous), while the sub-columnar connective tissue normally contains a certain number of plasma cells, and is, of course, devoid of hair follicles and sebaceous glands. The normal sub-squamous tissue is entirely free from plasma cells, while hair follicles and sebaceous glands are only found in that part (external to the sphincter ani muscle) which is covered by dry squamous epithelium.

It follows from what has been said that three different composite types of tissue were made the subject of investigation—

(1) Rectal tissue (*a*) covered with columnar epithelium, (*b*) possessing tubular glands lined with columnar epithelium and secreting mucus, (*c*) showing a loose sub-epithelial

tissue in which plasma cells are present, and (*d*) presenting a well-marked layer of involuntary muscle.

(2) Anal tissue (*a*) covered with *moist* squamous epithelium several layers of cells deep, sharply defined from the columnar epithelium of the rectum, (*b*) showing a moderately dense sub-epithelial connective tissue devoid of plasma cells or epithelial structures, and (*c*) possessing a well-marked muscular layer, proximally involuntary, but ending distally in the voluntary sphincter ani muscle.

(3) Cutaneous tissue (*a*) covered by *dry* squamous epithelium two or three layers of cells deep, (*b*) showing a dense sub-epithelial connective tissue devoid of plasma cells, (*c*) showing epidermal structures in the form of hair follicles, sebaceous glands and their ducts, and (*d*) presenting muscular tissue of the voluntary type in the muscles of the under-surface of the tail.

The anal tissue forms a ring that extends upwards for a distance of 2·5 mm. from the sphincter muscle with great constancy in medium-sized rats such as were used for the research.

The "Radium Dose."—Two tubes of radium were available for the experiment, which had the advantage of differing widely, yet not too widely, in respect of the quantities of radium they contained, and in other respects were closely similar. Tube A contained 38 mgr. $RaBr_2 \cdot 2H_2O$; it was of platinum ·3 mm. thick, and measured 25 mm. long by 2 mm. in diameter. Tube B contained 92 mgr. $RaBr_2 \cdot 2H_2O$; it was of platinum ·5 mm. thick, and measured 18 mm. long by 3½ mm. in diameter.

Experiments were made with Tube A (38 mgr.) to determine what length of exposure would be most suitable for the investigation, and it was found that 30 minutes' exposure gave satisfactory results. Making correction for the difference in thickness of the platinum tube, it was found that 13½ minutes' exposure to Tube B (92 mgr.) gave the same amount of ionisation, i.e., afforded the same "radium dose."

With the exception, therefore, of two rats to be mentioned subsequently, all the animals received the *same "radium dose,"* but they were divided into two series, (A) that with smaller quantity of radium acting for a greater length of

time (38 mgr. for 30 minutes), and (B) that with larger quantity of radium acting for a shorter length of time (92 mgr. for $13\frac{1}{2}$ minutes).

Method of Experiment.—A cotton thread was fixed by a clove hitch around the radium tube at a point equidistant from the two ends excluding the perforated solid partition. The tube was inserted into the rectum until the cotton thread was at the anal aperture, and was kept in position by means of a soft iron wire passed through the perforated end of the tube and turned once or twice around the root of the tail. An animal of each series was killed on the 1st, 2nd, 3rd, 7th, 8th, and 9th days (and in one series the 5th, 14th, and 21st days in addition) after exposure to radium, by breaking the neck. The lowest 25–30 mm. of the rectum and contiguous 5–7 mm. of the skin of the under-surface of the tail were immediately dissected off, the bowel was opened up, and the whole, pinned out on cork, was immersed in Carnoy's fluid for 20 minutes, passed through 4 changes of absolute alcohol, removed from the cork, and passed through 2 changes of xylol. A strip 30 mm. long by 4 mm. wide was then cut from end to end of the mass of tissue, to include 25 mm. upwards and 5 mm. downwards from the sphincter muscle. This strip was embedded in paraffin and cut along its long border so as to present all the varieties of tissue and cell mentioned above in one histological specimen. The sections were uniformly 5 μ thick.

It will be seen from the description that in addition to tissue which had been directly in contact with the radium

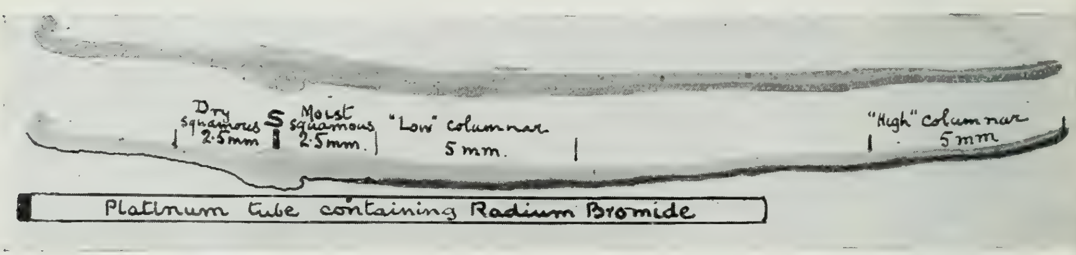


FIG. 1.—Photomicrographs of two sections of rectum and under-surface of skin of tail (rat). The epithelial layers (squamous to left, columnar to right of figure) have been blackened for clearness in the lower section, and details have been added indicating the nature of the experiments. S = Sphincter ani muscle

tube, rectal tissue is present which had been acted upon by radium at a distance. This is shown by Fig. 1, a microphotograph of two histological specimens, upon the lower of which the epithelium has been blackened, and certain details have been written for greater distinctness.

Staining was either by dilute (3%) Ehrlich's hæmatoxylin, or by Pappenheim's stain. Of these, Pappenheim's stain is more satisfactory for mitotic figures, and is essential for plasma cells. Unfortunately the superiority of Pappenheim's stain in the enumeration of mitotic figures was unknown to me until the research was half completed, otherwise it alone would have been used for this purpose. Actually, 5 specimens stained with hæmatoxylin, and 1 specimen stained with Pappenheim's stain, were used for the determination of each mean number of mitoses given in Table I. Had Pappenheim's stain been used throughout the values would have been somewhat higher.

In counting mitosis difficulty arises owing to the different positions of cells, and in some degree owing to the different stages of mitosis met with in a single section. For this reason I have counted each *focus* of chromatin in mitosis as a unit, with the result that the somewhat rare instances showing the diaster stage in profile have been counted as *two mitotic figures*. As this procedure has been adopted throughout the mean values given for mitosis are susceptible of comparison.

RESULTS OF EXPERIMENTS.

(A)—Experiment using 38 mgr. Radium Bromide for 30 minutes.

I.—The Columnar Epithelium, excluding Mitotic Changes.

1st Day Specimen.—The columnar epithelium, whether lining the tubules or superficial, is well preserved, but some tendency to desquamation of superficial cells is discernible in that part which was in contact with the radium tube. The cytoplasm is granular and swollen, and there is decidedly less formation of mucus, as evidenced by the number of goblet cells, than normal. The nuclei are larger than normal, sharply outlined and clear, the chromatin being apparently collected chiefly at the periphery.

2ND DAY SPECIMEN.—The appearances are similar, but desquamated cells entangled in mucus lie on the surface at the upper end. Goblet cells are numerous and large at the upper portion of the section, but are scanty near the anus.

3RD DAY SPECIMEN.—Cells swollen and granular; mucus formation moderate; small tracts of superficial epithelium are detached towards the upper part of the section.

5TH DAY SPECIMEN.—Many goblet cells except close to the junction with squamous epithelium, the central portions of some of the tubules being largely broken down into mucus. Mucus formation is more pronounced in the higher portions of the section. Nuclei of the cells are markedly swollen and clear. Margins of cells indistinct, cytoplasm granular.

7TH DAY SPECIMEN.—A few isolated superficial cells have undergone desquamation. Mucus formation little marked. Nuclei of cells still relatively free of chromatin in the centres, no swelling of nucleus.

8TH DAY SPECIMEN.—Nuclei throughout are apparently normal, but the cytoplasm of cells in the lower region is still granular and the cell margins are indistinct. Mucus formation is pronounced, and mucus is present at the openings of some of the tubular glands.

9TH DAY SPECIMEN.—Cells granular and without distinct margins throughout the specimen. Nuclei somewhat swollen and pale. Mucus formation pronounced. No desquamation of superficial cells is evident.

14TH DAY SPECIMEN.—Margins of cells frequently recognisable where not obscured by goblet-cell formation. Nuclei still somewhat swollen and pale, especially in the lower part of the section. Mucus formation a marked feature.

21ST DAY SPECIMEN.—General features of columnar cells indistinguishable from those of normal specimens.

It appears, therefore, that when 38 mgr. of radium bromide act upon the columnar cells of the rectum of the rat for 30 minutes changes occur in respect of cytoplasm, nucleus, and mucus formation. The cytoplasm rapidly becomes granular and the edges of the cells indistinct; the nuclei swell up and become clear and pale, the chromatin being chiefly arranged at the periphery of the nucleus. Desquamation of isolated

cells or small tracts of cells occurs. Mucus formation appears to be diminished at first, but later an excessive formation takes place. These changes are at their height and are most marked where the cells were in contact with the radium tube about the 5th day after irradiation, after which a return to normal slowly takes place. Reference to mitotic changes in the nuclei is reserved till later.

II.—**The Squamous Epithelium, excluding Mitotic Changes.**

1st Day Specimen.—*Moist variety:* The cell outlines are clear, the nuclei are very swollen and clear for the most part, but some are shrunken and leave a clear space between them and the cytoplasm. The superficial layers of epithelium are loosened. *Dry variety:* The changes are in general similar to those present in the moist variety, but the swelling of nuclei is less marked; desquamation of superficial keratinised layers has taken place.

2nd Day Specimen.—*Moist variety:* Nuclei very clear, pale, and swollen; superficial layers loosened. *Dry variety:* Nuclei stain very badly, but outlines are sharp; desquamation of superficial layers.

3rd Day Specimen. — Both varieties show the same changes as before, and in both nucleoli are very large and distinct.

5th Day Specimen.—As 3rd day.

7th Day Specimen.—*Moist variety:* Outlines of cells indistinct, less swelling of nuclei than in previous specimens. *Dry variety:* Outlines of cells fairly distinct; most of the nuclei are pale and swollen.

8th Day Specimen.—*Moist variety:* The nuclei are pale and there is some desquamation of superficial layers; the cytoplasm is granular and outlines of cells somewhat indistinct. *Dry variety:* The nuclei are swollen and represented by colourless ovals with blue margins; a single layer is present, and there is much desquamation of superficial layers of keratin.

9th Day Specimen.—*Moist variety:* Outlines of cells still a little indistinct. The nuclei are pale, but not so transparent, while in more superficial layers they stain as well as in the basal layer. *Dry variety:* As in 8th day specimen;

the outlines of the cells are very indistinct, and staining is very poor.

14TH DAY SPECIMEN.—*Moist variety:* The chromatin is distributed fairly evenly through the nucleus; the basal cells and nuclei are of their normal oval shape; the nuclei of more superficial cells are somewhat clear. *Dry variety:* Nuclear staining perhaps a little better than in the 9th day specimen. Desquamation of superficial layers.

21ST DAY SPECIMEN.—Cells and nuclei are indistinguishable from normal in the case of both varieties of squamous cell.

Squamous epithelium exposed to the action of the gamma rays from 38 mgr. radium bromide for 30 minutes, therefore, differs in its reaction according as the moist or the dry variety is considered. The effect on both varieties is similar in kind and consists in an alteration of the nuclei, which become swollen, clear, and stain badly, and in a modification of the cytoplasm whereby its connection with neighbouring cells is loosened and desquamation of tracts of keratinised cells occurs. But though the effects are similar the degrees to which they are evident is different, for the moist variety is less altered from the normal than the dry variety. Thus in the 9th and 14th day specimens the moist variety is practically normal, while the cells of the dry variety are still profoundly changed.

III. — **Epidermal Structures** (hair follicles, sebaceous glands). Of course these are only found in connection with dry squamous (cutaneous) cells, but one large sebaceous gland is found just internal to the sphincter ani muscle. Specimens stained on the 1st, 2nd, and 3rd days after irradiation showed the sebaceous cells somewhat swollen, while their nuclei and the nuclei of cells in the hair follicles stained poorly. In specimens from the 5th day onwards the appearances were similar to the normal except that the formation of sebum seemed to be excessive. It is noteworthy that in no instance were inflammatory changes found in the structures under consideration.

IV.—**Muscular Layers.** In the intestine the longitudinal coat, the circular coat, and the muscularis mucosæ (longitudinal) are well marked and are unstriated; beneath the

cutaneous epithelium are to be found longitudinal fibres of striated muscle. The chief changes noted were in the circular coat near the anus and in the sphincter ani itself. Over all the specimens of the experiment a granular and œdematous condition of the muscle in these positions was noticeable, and was most marked in the 3rd, 5th, and 7th day specimens. The muscle nuclei were swollen and clear. In the 14th day specimen some granular and œdematous change was noted in both the situations under consideration, but in the 21st day specimen the sphincter ani muscle appeared to be normal, whereas the circular coat of the lower part of the rectum was still granular and œdematous. The longitudinal muscle fibres in the lower part of the gut invested with the columnar epithelium showed a general paleness in staining of nuclei, but no great differences otherwise were noted. The muscularis mucosæ though nearer to the radium tube showed, throughout, less obvious change in cells and in nuclei than the circular coat.

The muscular coat in the highest region of the specimens was in good condition except in the specimens of the 3rd and 5th day, when the nuclei were clear and swollen and the muscle bundles were broken in the circular coat; a certain amount of hyaline change was noted in the 5th day specimen, but this has been observed in intestine from normal rats. No changes were noted in the longitudinal fibres. The striated muscle of the root of the tail was in uniformly good condition in all specimens except that of the 2nd day after irradiation. In this specimen striation was distinctly poor.

It would thus appear that unstriated muscle was more affected than striated, and that the circular coat in immediate association with the radium tube showed the greatest variation from the normal. The changes consisted in œdema and granular degeneration with alteration of nuclei so that they became swollen and clear.

(B) Experiment using 92 mgr. Radium Bromide for 13½ minutes.

I.—The Columnar Epithelium, excluding Mitotic Changes.

1st Day Specimen.—The cells of the lower part of the section show poor outlines, but the cytoplasm is not granular;

the nuclei are pale but chromatin appears to be evenly distributed, and the nuclei are not swollen. The number of goblet cells is small. No mucus is found on the surface and there is no desquamation of superficial cells. The cells of the high part of the section show some swelling of nuclei and a little loosening of superficial cells. The number of goblet cells is normal.

2ND DAY SPECIMEN.—Much mucus covers the surface in the lower part of the section; the tubules are profoundly altered, being practically converted into bags of mucus, the cellular cytoplasm, therefore, has almost disappeared. The nuclei are very swollen, transparent, and irregular. At the highest part of the section there is little mucus on the surface. The nuclei of the cells are clear and swollen, and the cytoplasm is swollen and hyaline in appearance. Goblet cells are numerous.

3RD DAY SPECIMEN.—A certain amount of mucus bathes the lower part of the section; the nuclei are swollen, clear, and very irregular in shape; the cytoplasm is much broken up. A considerable amount of mucus is present and many goblet cells. High up the nuclei are clear, swollen, and transparent, the chromatic substance being confined to the nuclear membrane; the outlines of the cells are fairly marked and the cytoplasm is coarsely granular. No desquamation of superficial cells is present. Goblet cells are numerous.

7TH DAY SPECIMEN.—Below, there is much mucus on the surface of the intestine, with extensive desquamation of tracts of superficial epithelium. The nuclei of the cells are clear, swollen, and irregular; the cytoplasm is swollen. Not many goblet cells are present. Above, the outlines of the cells are fairly marked, the nuclei are slightly swollen, but the chromatin appears to be evenly distributed. Few goblet cells are present.

8TH DAY SPECIMEN. — Below, the surface shows the presence of a little mucus; cell cytoplasm and nuclei appear granular and hazy. The nuclei stain evenly. Above, the nuclei are perhaps a little clearer than normal; very little mucus bathes the surface. Goblet cells are present in normal numbers.

9TH DAY SPECIMEN.—Below, the surface shows much mucus mixed with many desquamating cells. The columnar cells themselves are greatly swollen, the nuclei are very transparent and swollen. Above, traces of mucus bathe the surface, the cytoplasm is not swollen, the nuclei are pale and a little swollen. Many goblet cells are present.

From the above description it appears that considerable changes have taken place in the columnar epithelium over the region which was in contact with the radium tube. These changes are of a pronounced degenerative type and consist in mucoid degeneration of the cells with much desquamation, and alteration of the cell-nucleus. The change is pronounced already in the 2nd day specimen, and is still marked in the 9th day specimen.

The columnar epithelium at a little distance from the radium tube shows similar changes, but they are much inferior in intensity except as far as concerns the formation of goblet cells. Although the amount of mucus and mucoid degeneration appears to be greatest in the lower part of the section, definite goblet cell formation appears to be greatest higher up.

II.—The Squamous Epithelium, excluding Mitotic Changes.

1ST DAY SPECIMEN.—*Moist variety:* The cell outlines are good, and cytoplasm stains well; the nuclei are pale and swollen and show a granular chromatin: frequently they have contracted and are surrounded by a clear space. The superficial layers of keratinised cells have desquamated. *Dry variety:* Cell outlines are good, the nuclei are clear, swollen, and stain but faintly.

2ND DAY SPECIMEN.—*Moist variety:* The outlines of the cells are good, but nuclei are pale, clear, and swollen. *Dry variety:* The outlines of the cells are ill-defined, the nuclei stain badly, are clear and swollen, or contracted; desquamation of superficial keratinised layers has taken place.

3RD DAY SPECIMEN.—*Moist variety:* Desquamation of superficial layers, outlines of cells clear, nuclei large, clear and somewhat swollen.—*Dry variety:* Desquamation has occurred of superficial layers. Cytoplasm is granular and ill-defined, nuclei are clear and often contracted; the cells take the stain poorly.

7TH DAY SPECIMEN.—*Moist variety:* The definition of the cell outline is poor, nuclei are clear, swollen, but frequently contracted : some desquamation has occurred. *Dry variety:* Though some of the cells and nuclei stain badly, and the nuclei appear to be slightly swollen, the general appearance is fair.

8TH DAY SPECIMEN.—*Moist variety :* Slight desquamation of superficial layers. Cell outlines are good ; the nuclei show general distribution of chromatin, but some of them are contracted. *Dry variety :* The general appearances are good and could not be distinguished from the normal.

9TH DAY SPECIMEN.—*Moist variety:* On the whole the nuclei are normal in appearance, though some are abnormally transparent ; the cellular outline is fairly defined. Slight desquamation of superficial layers has occurred.—*Dry variety:* The nuclei are pale, but otherwise the epithelium appears normal.

From the above description it appears that squamous epithelium acted upon by the gamma rays of 92 mgr. radium bromide for 13½ minutes shows slight changes which chiefly concern the nuclei. These become swollen and take the stain poorly. The changes affect both moist and dry squamous varieties, but are more marked and persist longer in the case of the moist variety. Desquamation of superficial keratinised layers occurs in each variety. Specimens removed on the 7th, 8th, and 9th days after exposure to radium do not differ greatly from the normal in appearance.

III.—**Epidermal Structures.** Specimens taken the 2nd and 3rd days after irradiation showed a great formation of sebum within the cells of the sebaceous glands, the nuclei being on the whole normal in appearance, though staining poorly and being swollen in some cases. In the 7th day specimen the sebaceous gland cells were practically broken down into sebum, but in the specimens of the 8th and 9th days the sebaceous glands appeared normal. With the exception of somewhat poor staining, the cells of the hair follicles appeared to be normal.

IV.—**Muscular Layers.**

1ST DAY SPECIMEN.—In the upper columnar region the fibres of the circular coat were approximately normal,

but the nuclei appeared somewhat clear and swollen. The longitudinal fibres of the muscularis mucosæ and of the longitudinal muscular coat were very poor, the outlines of the cells being indistinct and the layers broken up to a considerable extent; the nuclei were irregular in shape and stained badly. In the lower columnar region the circular muscle was granular and œdematous, the outlines of the muscle bundles were lost, the nuclei were clear and swollen. The longitudinal fibres both sides of the circular muscle were much broken, staining was poor, the nuclei being practically unstained. Of the two systems of longitudinal fibres, that of the muscularis mucosæ was the worse. The sphincter ani showed the muscular fibres highly granular and the nuclei variable in size. Striated muscle of the tail was in a condition of "cloudy swelling," except that the nuclei were not unduly distinct, striation was just recognisable.

2nd Day Specimen.—In the upper columnar region the condition of the circular muscular coat was good, the longitudinal muscular coat was fair, but the longitudinal fibres of the muscularis mucosæ were somewhat granular and broken. All the coats were thin. In the lower columnar region the condition of the longitudinal (external) coat was good, the circular coat showed slight œdema and granularity, the fibres of the muscularis muscosæ were ill-defined and the nuclei very clear and contracted. The sphincter muscle was in good condition. Striated muscle was cloudy, but striation was well visible.

3rd Day Specimen.—In the upper columnar region the circular coat was in good condition, but the nuclei appeared swollen, the external coat was poorly developed, the fibres were cloudy, but the nuclei appeared normal. The muscularis muscosæ showed swelling of fibres, and the nuclei were œdematous, with poor staining and wrinkling of the nuclear membrane. In the lower columnar region the condition of the external coat was good, the circular coat was slightly granular and œdematous, the nuclei being very clear and contracted; the muscularis mucosæ showed some swelling and fracture of fibres, but was otherwise in good condition. The sphincter muscle was in good condition. Striated muscle was very cloudy, striation being only just visible.

7TH & 8TH DAY SPECIMENS.—The general appearances of all layers in all the situations were as above, but less marked, except in the cases of sphincter muscle and striated muscle. The sphincter muscle remained in good condition, but striated muscle of the 7th day specimen was more profoundly changed than at any other period, the fibres being much swollen and very granular; this obtained to such an extent that striation was almost invisible. In the 8th day specimen the striated muscle condition was better; the fibres were still cloudy, but striation was distinctly visible though the bands were broader than normal.

9TH DAY SPECIMEN.—The only noteworthy variations from normal concern the muscularis mucosæ in the lower columnar region (where the fibres were more widely separated than normal) and striated muscle. The latter was still cloudy, but striation was more sharply defined than in any specimen except that of the 2nd day.

From these descriptions it appears that the gamma rays of 92 mgr. of radium bromide acting for 13½ minutes induced changes in muscular tissue. These changes were chiefly manifest in the muscularis mucosæ and in striated subcutaneous muscle of the tail. Circular muscle fibres, whether of the rectum or the sphincter ani, showed some granularity and œdema, but on the whole were relatively little changed. The modification of striated muscle was very great in all the specimens, but appeared to be passing off on the 9th day after irradiation, by which time, however, the other muscular systems were normal.

Mitotic and Plasma Cell Changes.—The changes that have been described above after irradiation, though frequently marked, are not susceptible of numerical determination. In the case of mitosis and plasma cells, however, special staining reactions enable the changes to be placed upon a less personal basis. Nevertheless, even in the case of mitotic and plasma cell counts the personal factor cannot be entirely excluded. In a series of control counts of mitoses made for me by one of my colleagues, the values obtained were uniformly larger than those obtained by myself over the same fields of the same sections. In the case of plasma cells the personal factor is even greater. Besides the personal factor there occur

individual variations in the animals used for experiment, as can be seen by the variations obtained in four normal rats (Table I.), both for mitosis and for plasma cells. It follows that it is not justifiable to draw any deductions but those in which a clear tendency is discernible, in order that a fictitious degree of accuracy may not attach to the presentation of figures.

The actual mean numbers obtained in the different animals used in the research per millimetre of histological section 5 μ thick are set out in Table I., but a better judgment as to the actions upon the different types of epithelial cell and upon the sub-epithelial connective tissue can be obtained from consideration of Table II. In this table the experimental values have been collected into two groups dealing with animals killed respectively on the 1st, 2nd, 3rd, and on the 7th, 8th, and 9th days after exposure to radium, and the mean values thus obtained have been expressed as multiples or sub-multiples of the mean value for the normal. For example, Table I. shows that the mean number of mitotic figures per millimetre in a section 5μ thick for high columnar epithelium is in normal rats 3·6, whereas (under condition A) in the experimental rats of days 1, 2, and 3 the mean value was 17·3, and in the experimental rats of days 7, 8, and 9 was 14·8. Dividing 17·3 and 14·8 by 3·6 we obtain 4·8 and 4·1 for Table II. The other values have been dealt with similarly.

(A)—Radium dose=38 mgr. for 30 minutes.

In the region actually in contact with the radium tube it is seen that during days 1–3 mitoses in columnar cells are reduced to ·68, in moist squamous to ·5, and in dry squamous to ·15 of the normal, whence it follows that under this method of applying the radium dose columnar cells are slightly injured in respect of proliferative activity, dry squamous cells are greatly injured, moist squamous cells occupy an intermediate position. During days 7–9 recovery of columnar and of moist squamous cells is manifest, mitosis in the columnar cells being even greater than normal; dry squamous cells appear even more damaged in proliferative activity than during the earlier period. Columnar cells at a small distance from the radium tube (high) show well-marked increase in

TABLE I.

Days after Radium	N₁	N₂	N₃	N₄	Mean of normal	1	2	3	Mean 1–3	5	7	8	9	Mean 7–9	14	21	
						Experimental.											
(High) Columnar Mitoses ...	3·3	3·5	2·5	8·7	3·6	14·6	21·6	15·8	17·3	7·2	24·4	6·2	13·8	14·8	6·2	5·8	A
						2·2	12·6	5·7	6·8	—	13·8	6·3	28·4	16·2	—	—	B
Plasma cells	19·8	8·4	33·6	35·8	24·4	39·2	84·6	39·6	54·3	63·8	149·0	38·4	89·6	92·3	42·4	39·4	A
						37·2	18·2	34·0	27·8	—	40·2	42·8	76·8	53·2	—	—	B
(Low) Columnar Mitoses ...	8·9	9·3	7·3	14·0	9·9	4·3	10·0	5·8	6·7	8·3	15·5	4·3	20·1	13·3	13·0	9·2	A
						0·4	0·9	2·8	1·4	—	9·2	3·2	26·7	13·0	—	—	B
Plasma cells	15·0	10·4	37·4	9·2	18·0	45·0	66·8	14·8	42·2	26·2	41·2	31·2	31·2	34·5	47·6	45·6	A
						15·8	5·2	24·6	15·2	—	26·4	47·8	63·2	45·8	—	—	B
Moist Squamous Mitoses ...	0·7	0·9	1·12	1·92	1·16	0·6	0·72	0·32	0·55	1·52	1·48	0·28	1·0	0·92	1·24	1·4	A
						1·12	0·92	1·6	1·21	—	1·52	2·48	3·52	2·51	—	—	B
Plasma cells	0·4	0·4	0	0	0·2	2·4	4·4	0	—	0·4	1·6	0·8	0·4	—	0·4	0·4	A
						0	0·8	0	—	—	0	0	2·0	—	—	—	B
Dry Squamous Mitoses ...	1·8	2·3	3·0	1·92	2·26	0·4	0·4	0·2	0·3	0·12	0·4	0·12	0·2	0·24	0·4	0·7	A
						1·68	1·6	0·6	1·3	—	0·92	4·48	1·4	2·27	—	—	B
Plasma cells	0	0	0	0	0	0	0	0	—	0	0	0	0	—	0	0	A
						0	0	0	—	—	0	0	0	—	—	—	B

NOTE.—A = 38 mgr. $RaBr_2 . 2H_2O$ in ·3mm. Platinum for 30 minutes.
B = 92 mgr. „ „ ·5mm. „ „ 13½ „

Table II.

Days after Radium	Days 1–3.			Days 7–9.		
	38 mgr. for 30 min.	92 mgr. for 13½ min.	Indication for Treatment.	38 mgr. for 30 min.	92 mgr. for 13½ min.	Indication for Treatment.
(High) Columnar						
Mitoses	× 4·8	× 1·9	92 mgr. for 13½ min.	× 4·1	× 4·5	*Nil*
Plasma cells	× 2·2	× 1·1	92 mgr. for 13½ min.	× 3·8	× 2·2	92 mgr. for 13½ min.
(Low) Columnar						
Mitoses	× 0·68	× 0·13	92 mgr. for 13½ min.	× 1·33	× 1·3	*Nil.*
Plasma cells	× 2·4	× 0·8	92 mgr. for 13½ min.	× 1·9	× 2·5	38 mgr. for 30 min.
Moist Squamous						
Mitoses	× 0·5	× 1·04	38 mgr. for 30 min.	× 0·8	× 2·2	38 mgr. for 30 min.
Plasma cells	Negligible		—	Negligible		—
Dry Squamous						
Mitoses	× 0·15	× 0·57	38 mgr. for 30 min.	× 0·1	× 1·0	38 mgr. for 30 min.
Plasma cells	Negligible		—	Negligible		—

Platinum tube containing Radium.

mitotic activity, being five times as many as the normal in the 1–3 day period, and still four times as many as normal in the 7–9 day period.

So far as concerns plasma cells, the (low) columnar region in contact with the radium tube and that at a short distance (high) alone need consideration, the numbers of plasma cells in tissue covered with squamous epithelium (whether moist or dry) being negligible. During the 1–3 day period in both situations the number of plasma cells is rather more than doubled. During the 7–9 day period the plasma-cell infiltration of the sub-mucous tissue formerly in contact with the radium tube has undergone a slight diminution, but is still double the normal; in the region of intestine a little higher up the plasma-cell infiltration has become still further intensified, so that the plasma cells are four times as numerous as normal.

(B)—Radium dose=92 mgr. for 13½ minutes.

In the region actually in contact with the radium tube it is seen that during days 1–3 mitoses in columnar epithelium are reduced to ·13, in moist squamous epithelium are normal in number, in dry squamous epithelium are reduced to ·57; whence it follows that under this method of applying the radium dose columnar cells are profoundly injured in respect of proliferative activity, dry squamous cells are somewhat injured, moist squamous cells are not injured in the least degree. During days 7–9 recovery takes place so that the dry squamous cells proliferate as rapidly as normal, moist squamous cells and columnar cells even more rapidly than normal. Columnar cells at a small distance from the radium tube (high) show definite increase in mitotic activity, being 1·9 times the normal during days 1–3 and 4·5 times the normal during days 7–9.

So far as concerns plasma cells, the tissues covered with squamous epithelium may again be neglected. Considering the low and high columnar regions the numbers of plasma cells are about normal in the early period after irradiation (days 1–3), but are more than doubled during the later period (days 7–9).

SUMMARY OF CHANGES.

If the various changes in the different regions under the two contrasted methods of applying the identical radium dose be summarised, it is seen that considerable differences show themselves. This is seen below.

Columnar Region.—During the early period after irradiation (days 1–3) 92 mgr. for 13½ minutes produces the maximum interference with mitosis and the least inflammatory reaction at the site of contact with the radium tube, the minimum stimulation of mitosis and the minimum inflammatory reaction at a short distance from the radium tube. Further, general degenerative changes such as mucoid degeneration, formation of mucus, desquamation and alteration of nuclei are, with 92 mgr. for 13½ minutes, most pronounced in the region of contact with the radium tube; though present they are less marked at a little distance from the radium tube. Muscular tissue in the region was most profoundly affected in respect of the longitudinal fibres of the muscularis mucosæ, the circular and longitudinal muscles of the intestine being relatively little affected.

During the later period after irradiation (days 7–9) the 92 mgr. for 13½ minutes mode of application of the radium dose is still associated with the more profound changes, particularly as regards the occurrence of inflammation in the sub-columnar cells and the degenerative changes in the columnar cells and nuclei. Proliferative activity of the columnar cells is similar to that which obtains when 38 mgr. for 30 minutes have been applied.

Moist Squamous Region.—In this region the radium dose as applied in the 38 mgr. for 30 minutes form produces the maximum amount of alteration of the cells. The nuclei become swollen, clear, and stain badly, and the number of mitoses is reduced. A certain amount of actual desquamation of superficial layers is seen. The sphincter ani muscle, which lies in close relation to the moist squamous epithelium, is also more affected by this method of applying the radium dose. No recognisable inflammatory change is produced by either method of applying the radium dose.

Dry Squamous Region.—Here the 38 mgr. applied for 30 minutes produces the greatest effects, reducing mitotic

activity to a marked extent, and leading to swelling, transparency, and poor staining of the epithelial cells, with some desquamation of superficial keratinised layers of cells. Changes in the epidermal structures (sebaceous glands, hair follicles) and in striated muscle are less marked with this than with the method of applying the radium dose by means of 92 mgr. for $13\frac{1}{2}$ minutes.

In spite of the fact that the squamous epithelium regions offer a great contrast to the columnar epithelium regions in their reactions to the two types of applying the radium dose, it must not be assumed that the moist and the dry varieties of squamous epithelium behave exactly in the same way when considered *inter se*. Examinations of the various data show that dry squamous epithelium is more vulnerable than the moist variety. Thus 38 mgr. for 30 minutes reduces the mitoses in dry squamous epithelium to ·15 of the normal, but only reduces those of moist squamous epithelium to ·5. A similar difference in vulnerability is seen with an application of 92 mgr. for $13\frac{1}{2}$ minutes. This is true for the 1–3 day period, but the difference between the two types of epithelium to identical irradiation is equally seen when the values for days 7–9 are examined, for though in both instances it appears that the 38 mgr. for 30 minutes is more effective in reducing proliferative activity than 92 mgr. for $13\frac{1}{2}$ minutes, the moist squamous variety is less profoundly affected in this direction than the dry. Indeed, the moist squamous cells under 92 mgr. for $13\frac{1}{2}$ minutes' irradiation now show that the *reduced* proliferative activity has given place to an actual stimulation, the number of mitoses being double the normal.

Indications for Treatment in Cases of Carcinoma.—In the treatment of patients it is clear that attention must be paid, not only to the actual epithelial cells which form the characteristic feature of the new growth, but also to the stromal tissue in which those cells are embedded and the normal tissues which may be in the immediate neighbourhood of the growth. Hence it is necessary to consider the types of epithelial cells, with the peculiar types of sub-epithelial tissue, the peculiar types of muscular tissue (and any specialised epithelial structures which may be present), as complexes. Clearly it would be little advantage to destroy the malignant

epithelial cells if the normal elements of the complex were so profoundly changed as to be incapable of recovery. The desideratum is maximal injury to malignant cells with minimal injury to non-malignant structures that are closely bound up with the malignant growth.

It appears from the experiments that the probability of inflicting damage on the epithelial cells without injuring other tissues is far greater in the case of dry squamous epithelium than in the case of moist squamous epithelium, and in the case of both of these is far greater than in the case of columnar epithelium. Irradiation of columnar epithelium, indeed, always appears to bring in its train an inflammatory reaction of the sub-mucous tissue. Nevertheless, the mode of application of a given radium dose is of great importance. The radium dose being a product of two factors—quantity of radium and length of exposure—they may be varied indefinitely in inverse directions without altering the "radium dose." But the experiments show with the greatest clearness that the same arrangement of time and quantity in a radium dose produces very different effects when acting upon the three types of epithelial tissues (considered as complexes). Hence the optimum arrangement of radium dose for the treatment of a columnar cell carcinoma with its attendant tissues is different from the optimum arrangement for treating a carcinoma of dry squamous epithelium with its attendant tissues. The experiments show that maximal effects on the epithelial cells and minimal effects upon the associated tissues are produced, in the case of a columnar cell growth, when quantity of radium is relatively great and length of exposure of the tissues is relatively small, but is produced, in the case of a dry squamous cell growth, when the quantity of radium is smaller and the length of exposure to the rays is increased.

From the experiments no indication is given as to the actual quantity of radium or length of exposure that should be used in treatment of a carcinoma of dry squamous cell type. They indicate, however, with great clearness that if x mgr. of radium bromide acting for y hours produce optimum results of a cutaneous squamous cell carcinoma, *cæteris paribus*, x must be increased and y must be diminished

in order to obtain the optimum results in a columnar cell carcinoma.

In the case of carcinomata of moist squamous surfaces the indications are not quite clear. So far as concerns the epithelial cells themselves, probably the quantity factor x might remain as for cutaneous squamous cell carcinoma, the time factor y being prolonged, but it must be remembered that a carcinoma of a moist squamous surface is in close relation with sub-mucous tissue upon which increase of the time factor acts injuriously. Hence the indications differ according to the size and situation of the growth. If the growth be small and sub-mucous tissue be in close relation, the *time factor* should probably be kept as low as possible, and the quantity factor should be high. On the other hand, if the growth be large, and sub-mucous tissue be relatively at a distance, the *quantity factor* should be kept as low as possible and the time factor should be raised.

Regarding the columnar cells and sub-mucous tissues on the one hand, and the squamous cells and sub-cutaneous tissues on the other, as complexes, and considering the total action of radium doses eight times as great as those previously dealt with, it is seen that the time and quantity factors of the radium dose play the contrasting parts which have already been mentioned. Thus in Fig. 2 are shown low magnifications of two preparations, the upper of which was exposed to 92 mgr. $RaBr_2$ for 108 minutes, the lower to 38 mgr. for 240 minutes. The radium doses were therefore identical considered in respect of the amount of ionisation they produced. The two rats were killed on the 9th day after irradiation. The changes induced in the tissues, however, are widely different, for in the specimen with 92 mgr. for 108 minutes' exposure (upper) the mucous membrane persists—though high magnification shows inflammatory and other changes—whereas in the specimen with 38 mgr. for 240 minutes' exposure (lower) the inflammation has been such that the mucous membrane in contact with the radium tube and a little beyond has entirely sloughed away. High magnification shows the remnants of the sub-mucous tissue crammed with inflammatory cells, notably polymorphonuclear leucocytes. But whereas in the case of the mucous and

FIG. 2. To show the effect of variation in the [illegible] quantity factors of constant [illegible] and subcutaneous tissue of rat. Upper section irradiated by 92 mgr. $RaBr_2$ for [illegible] minutes; lower, by 38 mgr. for 240 minutes. The [illegible] of the sections face one another. For description see text.

sub-mucous portion the smaller quantity of radium acting for the greater length of time has produced the more profound destructive changes, the exact converse is the case when the cutaneous and sub-cutaneous portion is examined, for here it is seen that the inflammatory reaction and destruction of squamous cells is greater in the case of the rat exposed to 92 mgr. for 108 minutes. Undesirable damage is better eliminated by keeping the quantity factor of the "radium dose" *high* and the time factor *low* in the case of the columnar cell complex, and is better eliminated by keeping the quantity factor of the "radium dose" *low* and the time factor *high* in the case of the squamous cell complex.

FURTHER OBSERVATIONS ON THE PRESENCE OF ALTMANN'S GRANULES IN EPITHELIUM IN CONTACT WITH CARCINOMA CELLS.

By WILBERFORCE SMITH.

THE present research is an extension of the observations recorded in the Twelfth Cancer Report (1913, p. 153). In that paper, invasion of endometrium by squamous cell carcinoma was considered. During the past year, carcinoma of the breast and of the large intestine have been made the subjects of a similar research. As before, attention has been directed to the apparently normal epithelial cells which were closest to the carcinoma.

METHODS.

The fixation and staining methods adopted were again those of Beckton.*

Six cases of spheroidal cell carcinoma, one of duct carcinoma, and one of perithelioma of the breast were examined. Strips of tissue two or three inches long were cut, radiating from the growth in different directions, and these were divided into a series of pieces which were fixed and embedded in paraffin. Of five cases of carcinoma of the large intestine, only three led to definite results. The piece of bowel, six to fourteen inches long, was cut open, pinned down, and frozen, and a strip cut along its entire length. From this a numerical series of blocks was prepared. In all cases serial sections 5 μ in thickness were cut, and every twentieth or thirtieth, or in some special cases every single section, was mounted and examined, consecutive sections being stained by the acid fuchsin, and by the hæmatoxylin and eosin methods respectively.

All types of cells in the neighbourhood of the carcinoma were examined as to Altmann's granules, and compared with

* Archives of the Middlesex Hospital, vol. xxvii., 1910. Ninth Cancer Report, p. 115.

similar cells at a distance from the growth, as well as with the corresponding cells in the next (serial) section stained with hæmatoxylin.

Results.

(1) Normal Variation in Granule Content of Cells.

That marked variation may occur in the number of granules present in cells of the same type, even in different parts of the same section, was emphasised in a previous paper (loc. cit., p. 154). Although this statement was made in reference to the richly granular epithelium of the endometrium, it is equally true in the case of the glandular epithelia of the breast and bowel, due regard being made to the fact that the latter normally contain far fewer granules than the columnar cells of the endometrium. Especially is this the case in the intestinal mucosa, large portions of which may be destitute of granules, in parts remote from the carcinoma. No corresponding change in histological detail, as revealed by other stains, appears to accompany this variation. There is occasionally, however, a corresponding but less complete absence of granules from the fixed cells of the stroma. No explanation of the phenomenon can be given.

Frequently amid the collections of carcinoma cells were many carcinoma cells which contained granules, and in one case entire columns of them were granular. Beckton has observed (loc. cit. p. 125) that degenerating (human) carcinoma cells show Altmann's granules, but the above remarks apply to cells in which no evidence of degeneration could be observed. Some of these sections were restained and differentiated by Beckton and myself, working separately, and similar results were obtained. It is to be noted that in mouse carcinoma, Beckton found that one third of the cases showed so many Altmann's granules as to appear non-carcinomatous, if judged by this test alone (loc. cit.).

(2) Granular Content of Cells contiguous to the Carcinoma.

(a) Breast.

The Epithelium of the Acini which were in contact with or even surrounded by carcinoma that was spreading chiefly along lymphatic planes, showed no change in its granular

content, so long as the acini were recognisable as such. In one or two cases, lobules were examined which showed proliferation and irregular arrangement in excess of that occurring in mastitis, but of uncertain character. From the cells of these Altmann's granules were absent, or few in number.

The Duct Epithelium, more consistently granular than the secretory cells, showed no variation whatever when traced, by means of serial sections, through masses of carcinoma cells. In places the latter undermined and insinuated themselves between the regular epithelial cells, from which they may be readily distinguished by their general appearance and complete absence of Altmann's granules. In no instance was it possible to presume the conversion of innocent into carcinoma cells by observing the disappearance of granules. On the contrary, typical epithelial cells singly or in small groups were frequently agranular, but showed no other resemblance to carcinoma cells in their vicinity. Similarly an absence of resemblance to carcinoma cells, when stained by ordinary methods, and, indeed, an unbroken basement membrane or muscularis mucosæ generally characterised any strip of epithelium the cells of which were granular.

Lymphatic Vessels were traced in several cases right through the carcinoma, which profoundly affected them, to a point of emergence at which they were again normal. They appeared to be invaded in various ways, but no consistent disappearance of granules in the endothelium was noted such as might be taken to indicate a process of malignant conversion. In several cases direct continuity was observed between a collection of carcinoma cells outside a lymph space, and the endothelium. Close examination of such a junction showed that perhaps two or three cells projecting into the lumen at that point were agranular, and resembled the carcinoma cells in size and shape, while the rest of the cells lining the lumen (endothelial cells) contained an average proportion of granules. In other cases a lymph space was surrounded by carcinoma cells, which multiplied till the lumen was almost obliterated; nevertheless it was still lined by a normal proportion of granular endothelial cells, whose general histological characters were unchanged.

In several cases a lymphatic vessel contained a mass of carcinoma cells showing degeneration changes of varying degree. Such masses were invariably found to be attached at some point to the vessel wall, the stalk and base being composed of agranular cells having the characters of carcinoma. The latter were traceable through the incomplete basement membrane into the stroma. Except at this site the whole lumen may be lined by granular epithelium, or carcinoma cells at the base may extend so far round as to leave only a small proportion of the lumen still lined by normal granular cells.

(b) Large Intestine.

It has not been possible to obtain a specimen showing an absolutely unbroken line of continuity between the innocent and the carcinoma cells. In cases, however, in which only a few cells at the mouth of a gland were wanting, it was possible to see that no disappearance of granules in the goblet epithelium occurred in the immediate neighbourhood of the carcinoma. Similarly, where the carcinoma has advanced in the sub-mucous and sub-epithelial connective tissue, so as to impinge upon the crypts of Lieberkühn, the cells lining these show no variation in granular content, nor in general histological appearance.

Conclusions.

1. The normal glandular epithelial cells of breast or large intestine show no variation in their complement of Altmann's granules, where such cells are in close contiguity with carcinoma of the part.

2. There is no indication, from the study of Altmann's granules in these tissues, that normal epithelium is converted into carcinomatous epithelium by direct contact with carcinoma cells.

MEASUREMENTS OF RADIUM RAYS AS USED CLINICALLY.

By S. RUSS.

THE nature and characteristics of the rays emitted by the members of the radium series have been studied in great detail, and one may find in the literature of the subject quantitative data applicable to the rays given out by each member from radium to its final radio-active product, polonium. If the relative intensities of the rays under all circumstances were accurately known it would be possible to express the composite radiation in terms of these individual quantities; this composite radiation is the immediate concern of those engaged in radium therapy, and the following measurements have been carried out in order to provide data from which the general characteristics of the rays actually used under various conditions may be clearly seen. These measurements have been confined to the beta and gamma rays; the alpha rays from radium do not penetrate to a greater depth than 0·1 mm. of any tissue, and would therefore only come into consideration if the radium were administered as a drinking water or by intravenous or subcutaneous inoculation. The beta and gamma rays are heterogeneous to a marked degree, and although the statement that the beta rays are much more easily absorbed than the gamma rays is generally true, the recent work of Rutherford and Richardson* has shown that some of the softer gamma rays from RaB are more easily absorbed by aluminium than are the harder types of beta rays. Since the separation of beta rays by a magnetic field is not a practical clinical issue, it is not possible to say under all circumstances exactly what types of rays are being used, but we are nevertheless able to say to what extent they are absorbed by the tissues.

* "Philosophical Magazine," 1913, p. 722.

The two chief methods by which radium is used clinically are, either to spread the radium over a flat applicator, or to insert the radium in a small metal tube (usually of platinum) of thickness varying from 0·3 mm. to 1·5 mm. or more. The flat applicator will first be considered. Varying with the thickness of varnish covering the radium, the radiation will consist of a varying quantity of beta and of gamma rays. When such an applicator is applied to the superficial tissues it is desirable to know how the intensity of the rays decreases in the successive layers of the tissue. It decreases because of the spreading out of the rays from the source, and also because of the absorption which the rays suffer as they make their way through the succeeding layers. It will be seen from the subsequent data that as far as the beta rays are concerned the absorption by the tissues determines this decrease in intensity very much more than the increasing distance does, but that the decrease in the gamma ray intensity is much more due to the distance effect than to the absorption that they suffer.

The radiation from a flat applicator has been studied in the following manner: A shallow cylindrical box of alu-

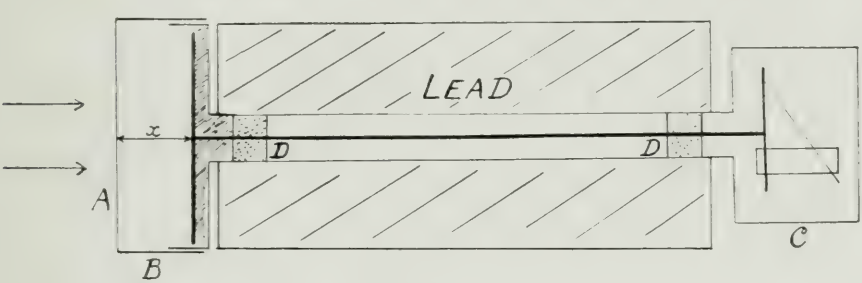


FIG. 1.

minium, 2 mm. deep and 4 cm. diameter, was provided with a mica window, thick enough to stop all the alpha rays. This box was filled with about 10 milli-curies,* and when the active deposit (RaA, RaB and RaC) had reached its equilibrium value, measurements were made of the composite radiation emitted from it. This was done in the following manner: The applicator was mounted in line with an ionisation

* One milli-curie is the amount of emanation in equilibrium with 1 mgr. of radium.

chamber (B) (Fig. 1) containing an aluminium disc which was connected by a wire running through the amber plugs (D. D) to a small gold-leaf electroscope (C). The rays entered B through a very thin aluminium window (A) (about 0·001 mm. thick) and ionised the air in this vessel, which was measured by the rate of movement of the gold leaf in C, the rays being practically excluded from C by an intervening mass of lead

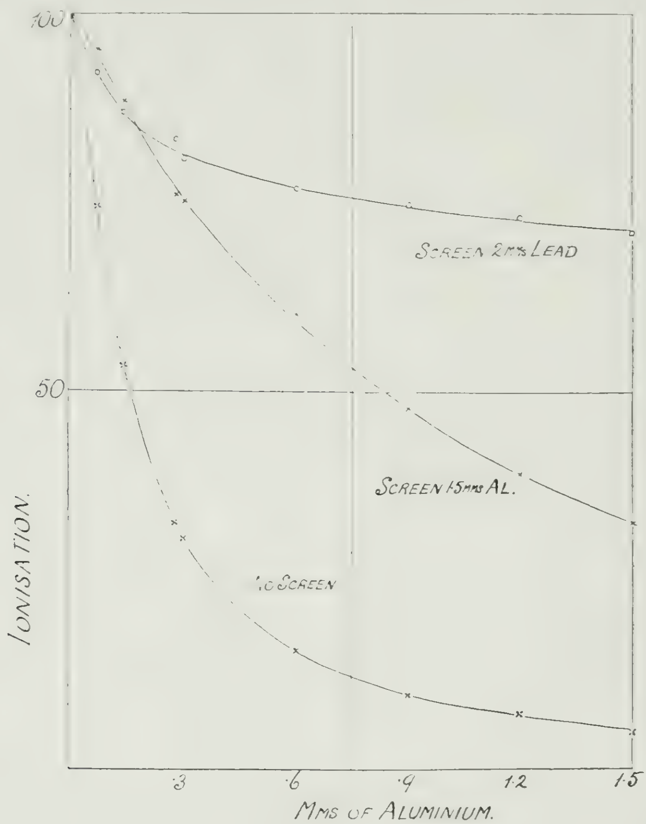


Fig. 2.

10·5 cm. thick. The cylindrical ionisation chamber (B) was 4 cm. diameter (the same as the applicator), and the depth (x) could be varied as required ; it was generally 1·2 cm.

The composite radiation from the unscreened applicator is very rapidly absorbed by aluminium sheets placed in front of the vessel B. This may be seen from the lowest curve (Fig. 2).

The ionisation is reduced to about one-tenth of its initial value in going through 0·9 mm. of aluminium. The applicator was now screened with 1·5 mm. of aluminium, and the character of the emergent rays again determined. From the middle curve of the same figure it will be seen that 0·9 mm. of aluminium now reduces the ionisation to 47·5 per cent. of its initial value, instead of to 10 per cent., as in the previous case; this part of the composite radiation is of moderate penetrating power (about that of X-rays from a bulb running at 5 to 6 cm. spark-gap, the softest rays excepted). The applicator was then screened with 2 mm. of lead, and a similar series of measurements made. The data of special interest here are those at the beginning of the top curve of the same diagram. They show that there is a soft component present (almost certainly secondary gamma rays produced in the lead), which actually makes the curve dip below the preceding one, although the bulk of the radiation, as the rest of the curve shows, is much more penetrating. The numerical data for these three cases of the composite radiation will be found in Table I.

TABLE I.—ABSORPTION OF COMPOSITE RAYS FROM FLAT APPLICATOR.

Thickness of aluminium.	No screen. Ionisation.	Screen 1·5 mm. aluminium. Ionisation.	Screen 2 mm. lead. Ionisation.
0 mm.	100	100	100
0·07	74·0	95·1	92·2
0·14	53·6	88·5	87·0
0·28	32·4	75·8	83·3
0·3	30·2	75·0	80·6
0·6	15·0	60·0	76·6
0·9	9·4	47·5	74·6
1·2	6·6	38·8	72·8
1·5	4·7	32·4	70·8
3·0	—		66·3
4·5	—	—	64·2
6·0	—	—	63·3
9·0	—	—	60·6

The Absorption of the Composite Rays by Tissues.

The heterogeneous nature of the composite radiation having been studied in aluminium, the extent to which the more easily absorbed of these rays (curves 1 and 2) penetrate various tissues has been found. The tissues were those of the sheep: they were mounted on wooden blocks, frozen, and thin layers (0·65 mm. thick) cut with a large size microtone

and then mounted on a thin mica frame in front of the window of the ionisation vessel. The absorption by the tissues of the unscreened rays from the applicator was first measured, and then when the rays were screened by 1·5 mm. of aluminium, the data for which are collected in Table II.

When these data are plotted out on diagrams the same general features are noticed as when the rays are absorbed by aluminium—viz., a very rapid absorption of the unscreened rays, which becomes less marked when the rays are screened. From the data it may be seen whether the tissues absorb the rays as their densities would suggest, and by direct comparison between the numbers with those for aluminium (Table I.) whether they are, weight for weight, such efficient absorbers. From the general trend of the decrease in ionisation in going through the same thickness of muscle, liver, spleen, &c., it will be seen that the denser the tissue the more it absorbs. After traversing about 3 to 3·4 mm. of these tissues the unscreened composite radiation is reduced to about 5 or 6 per cent. of its initial value.

TABLE II.—ABSORPTION OF COMPOSITE RAYS FROM FLAT APPLICATOR.

No screen.

Thickness of tissue.	Nature of Tissue				
	Muscle (density 1·25). Ionisation.	Liver (density 1·21). Ionisation.	Spleen (density 1·17). Ionisation.	Brain (density 1·12). Ionisation.	Fat (density 0·92). Ionisation.
0 mm.	100	100	100	100	100
0·65 „	32·5	36·0	36·7	36·8	40·2
1·30 „	—	18·0	—	—	—
1·95 „	10·3	11·4	12·4	12·2	13·0
3·25 „	4·5	5·4	5·8	5·7	6·4
4·55 „	2·3	3·5	3·1	3·5	3·4

Screen 1·5 mm. aluminium.

Thickness of tissue.	Muscle. Ionisation.	Spleen. Ionisation.	Brain. Ionisation.
0 mm.	100	100	100
0·65 „	85·5	90·0	–
1·95 „	62·0	56·2	57·0
3·25 „	43·0	41·4	36·6
4·55 „	26·3	29·9	26·7

A comparison of the absorbing powers of these tissues with that of aluminium is made by finding the reduction in the ionisation that a certain thickness of tissue causes, and

then finding from the bottom curve (Fig. 2) the thickness of aluminium which causes the same diminution in the ionisation. If the ratio of the thickness of tissue to that of aluminium is the inverse of their respective densities, then the tissue absorbs according to a simple density relation. This has been tested and the results collected in Table III.

TABLE III.

Tissue.	(a) Thickness of tissue. / Thickness of aluminium.	(b) Density of aluminium. / Density of tissue.	Ratio a/b.
Muscle	2·38	2·17	1·10
Liver	2·60	2·24	1·16
Spleen	2·79	2·32	1·20
Brain	2·75	2·42	1·14
Fat ...	2·91	2·94	0·99

The last column, which should be unity if the above density relation holds, shows that muscle and fat absorb the rays very nearly according to this simple density relation, but that for the other tissues aluminium is a rather more effective absorber, weight for weight, than they are, the spleen appearing to be the least efficient. The effect of any secondary radiation given out by the tissues would be to make them appear as less efficient absorbers. A similar procedure with the screened rays shows that the ratio a/b is 1·14, 1·22, and 1·07 for muscle, spleen, and brain respectively.

Absorption measurements are more easily and accurately made with a substance like aluminium than with tissues. When the coefficient of absorption (λ)* of some radiation has been found in aluminium, the above measurements indicate that no very serious errors would generally be introduced if the coefficient of absorption of these same rays in a tissue were reckoned from the simple relation—

$$\text{Coefficient of absorption in tissue} = \text{coefficient in aluminium} \times \frac{\text{density of tissue.}}{\text{density of aluminium.}}$$

In blood-containing organs such as spleen, liver, &c., however, this process would probably give rather higher values than the actual absorption coefficients.

* The coefficient of absorption (λ) is obtained from the relation

$$\lambda = \frac{2\cdot301 \times (\log._{10}Io - \log._{10}I)}{d}$$

where Io = initial intensity of the rays.
I = intensity after going through a distance d.

The Radiation from Radium in Platinum Tubes.

When salts of radium are enclosed in platinum tubes the radiation emitted is mostly of a penetrating character, a thickness of 0·3 mm. being sufficient to absorb all the soft, and a considerable proportion of the moderately penetrating beta and gamma rays. Even so, however, the composite

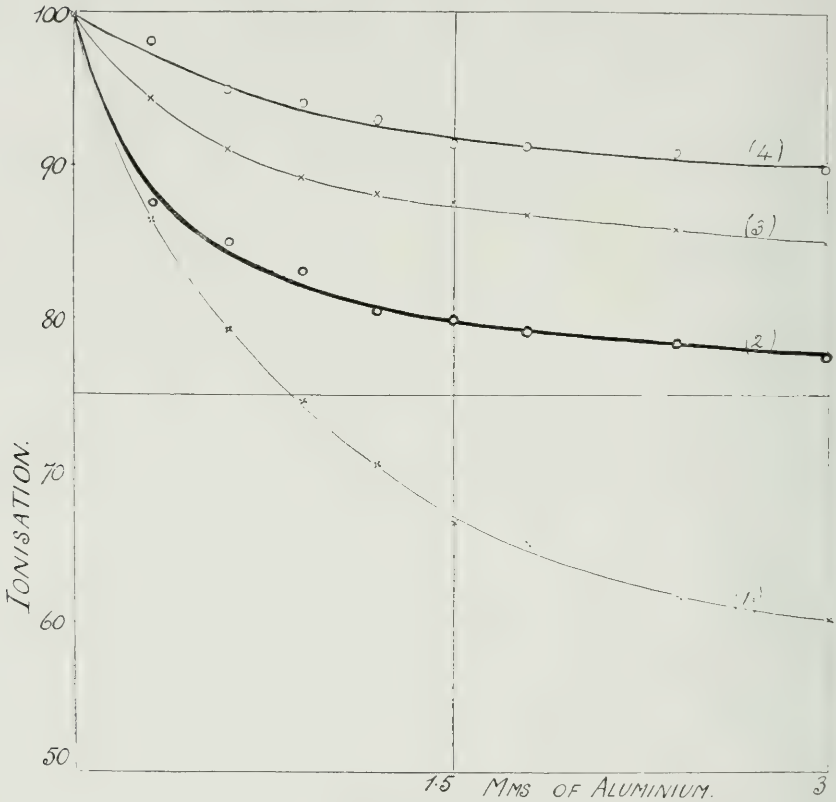


FIG. 3.

radiation through 0·3 mm. of platinum consists not only of the very penetrating rays but of some components which are only completely cut out by an additional 1·2 mm. of platinum (1·5 mm. in all, or 3 mm. of lead).

The method by which such measurements are made has already been indicated: the tube containing the radium is

mounted at a suitable distance from the ionisation vessel, and the gradual reduction observed when layers of aluminium are interposed between them. The general character of this radiation may be seen from curves (1) (2) (3) and (4) in Fig. 3, corresponding to thickness of platinum 0·3 mm., 0·5 mm., 1 mm., and 1·5 mm. respectively. Inspection shows that the rays emerging through 1·5 mm. are all of a very penetrating character. For a thickness of 1 mm. there is a small percentage of moderately penetrating rays. Curve 2 shows that for a thickness of 0·5 mm. (tubes of this thickness are very often used clinically) about 20 per cent. of the ionisation is due to the moderately penetrating rays. The effect of screening such a tube with an additional millimetre of platinum is to cut out all except the very penetrating rays. The presence of the moderately penetrating rays is more evident still when the platinum is reduced to 0·3 mm. The numerical data from which the curves are drawn are collected in Table IV.

TABLE IV.—ABSORPTION OF RAYS FROM PLATINUM TUBES.

Thickness of aluminium	(1) 0·3 mm. platinum. Ionisation.	(2) 0·5 mm. platinum. Ionisation.	(3) 1 mm. platinum. Ionisation.	(4) 1·5 mm. platinum. Ionisation.
0	100	100	100	100
0·3	86·5	87·5	94·5	98·2
0·6	79·2	85·0	91·2	95·0
0·9	74·4	83·0	89·2	94·0
1·2	70·2	80·5	88·2	92·9
1·5	66·4	79·8	87·5	91·6
1·8	65·0	79·0	86·8	91·3
2·4	61·8	78·2	85·8	90·7
3·0	60·0	77·2	84·8	89·6

The Diminution in Intensity of the Rays in Penetrating the Tissues.

Confining our attention to the two typical cases—viz., the flat applicator and the metal tube—if it were known how the radiation, apart from absorption, varies in intensity at different distances from the source, the data necessary for finding the intensity of the rays at any required depth in the tissues would be at hand. To determine the values of the radiation at different distances the same apparatus as in Fig. 1 was used, except that the depth (x) of the ionisation chamber was reduced from 12 to 3 mm., this being as shallow

as could be conveniently used. The flat applicator was then placed at distances 1, 2, 3 to 10 cm. away from the face of the ionisation chamber, and the respective values of the ionisation due to the beta rays observed. The values obtained are collected in Table V., the value at a distance 1 cm. being

TABLE V.—DECREASE OF RADIATION WITH DISTANCE.

No absorption.

Distance.	Flat applicator.	Tube.
1 cm.	100	100
2 ,,	64·8	60·5
3 ,,	43·8	38·4
4 ,,	31·2	25·8
5 ,,	22·7	18·2
6 ,,	17·0	13·7
8 ,,	10·7	8·4
10 ,,	7·7	5·8

taken as 100, and a small correction applied to the values at the other distances to allow for the absorption of the rays by the air between the applicator and the vessel. A similar series was obtained for the radiation from a small tube 2·5 cm. long placed at different distances along the axis of the same shallow ionisation vessel. These values, also corrected for the absorption of the air, are to be found in the same table. It will be observed that the radiation falls off more quickly from the tube than it does from the flat applicator.

To find the varying intensity of the rays as they go through some tissue of the density of water let us assume two typical clinical cases :—

(1) Radium in flat circular applicator, 4 cm. diameter, screened by 2 mm. of lead and the soft components (*vide* Fig. 2) cut out by a few layers of lint.

(2) Radium in platinum tube 1·5 mm. thick, 2·5 cm. long.

Case 1.—After going through 2 mm. of lead and the layers of lint the rays are still not homogenous but consist of moderate and very penetrating rays, with the result that the absorption coefficient in aluminium gradually diminishes. This was measured for varying thicknesses up to 9 mm., and by plotting logarithmically all the data in column 4 of Table I. it is found that after going through 3 to 4 mm. of aluminium—i.e., approximately 1 cm. of tissue—the rays are all of the very

penetrating type with a coefficient of absorption in aluminium of 0·142 cm.[1], and therefore in tissue $\frac{0{\cdot}142}{2{\cdot}71} = 0{\cdot}0524$ cm.[1] With the help of this number the data in Table VI. have been obtained showing the decrease in the ionising value of

TABLE VI.—ABSORPTION OF COMPOSITE RADIATION BY TISSUES.

Thickness of tissue.	Case 1. Flat applicator.	Case 2. Metal tube.
1 cm.	100	100
2 „	84·0	92·7
3 „	79·6	85·9
4 „	75·7	79·6
5 „	71·8	73·8
6 „	68·2	68·4
8 „	61·4	58·8
10 „	55·3	50·5

the rays after going through the given thicknesses of tissue, simply on account of the absorption. The value at 1 cm. is taken as 100, the value of 2 cm. is got directly from the absorption curve, Fig. 2, and the others calculated from the above coefficient.

Case 2.—A similar procedure has been carried through here: the rays which pass through 1·5 mm. of platinum are all of the very penetrating type with an "effective" coefficient of absorption in aluminium of 0·205 cm^{-1}, and therefore in tissue $\frac{0{\cdot}205}{2{\cdot}71} = 0{\cdot}076$ $cm.^{-1}$ The numbers given in the same table are calculated directly by means of this coefficient. (The different values of λ are due to the different experimental conditions.)

TABLE VII.—INTENSITY OF RADIATION AT DIFFERENT DEPTHS OF TISSUE.

Depth of tissue.	Case 1. Flat applicator.	Case 1. Metal tube.
1 cm.	100	100
2 „	54·6	56·0
3 „	34·8	53·0
4 „	23·6	20·0
5 „	16·3	13·0
6 „	11·6	9·4
8 „	6·6	4·9
10 „	4·2	2·9

The data are now available for finding the intensity of the rays at any particular depth of tissue for these two cases. If the radiation number, Table V., is multiplied by the corresponding absorption number, Table VI., the product gives the intensity of the rays at the depth in question. These values at each depth, that at 1 cm. again being taken as 100, are given in Table VII. and reproduced in Fig. 4. The radiation from the applicator diminishes less rapidly than that from the tube except for the first centimetre, in which the

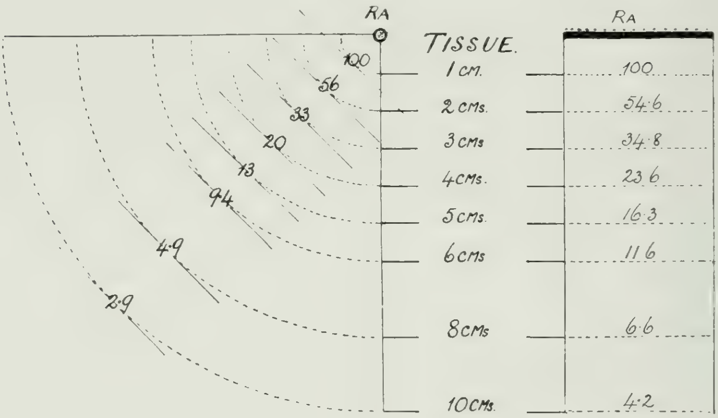


FIG. 4.

more absorbable rays are stopped. From the data given in Tables I. and IV. cases corresponding to different thicknesses of platinum and lead shields may be dealt with.

ON THE IMMUNITY CONFERRED UPON MICE BY RADIUM-IRRADIATED MOUSE CARCINOMA.*

By B. H. WEDD, A. C. MORSON, AND S. RUSS.

It has been shown by Wedd and Russ (1912[3]) that when the cells of mouse carcinoma (Twort strain) are irradiated *in vitro* by the β-rays from a source of radium bromide of intensity 2·2 mgr. per square cm., for periods of an hour and upwards, the tumour material does not grow when inoculated into normal mice. The question whether such irradiated but non-tumour forming material gives rise to any immunity was put to us by Dr. Murray, and the first part of the present paper provides an answer in the affirmative. The remainder of the paper is devoted to the possibility of some clinical application of this immunising action.

Immunity Produced by Irradiated Cells.

The technique adopted was as follows: Thin layers of tumour tissue were exposed to the radium for a definite period of time in the manner already described;† 0·1 c.c. of it was then inoculated into a number of medium-sized normal mice. After fifteen days the survivors were given a test inoculation of the same strain of tumour, small pieces of which were also inoculated into a number of normal mice. The numbers of tumours subsequently developing in the two sets of mice were directly compared. This procedure was followed for six different periods of irradiation.

The results obtained are collected in Table I., from which, and from the accompanying curve (Fig. 1), it will be seen that, whereas for the short periods of irradiation a considerable degree of immunity is conferred by the tumour tissue, this diminishes to an insignificant amount as the time of exposure is prolonged.

* Published in "Journ. Path. and Bact.," vol. xviii., 1914.

† Loc. cit.

It is relevant in this connection to recall the work of Contamin (1910[1]), who showed that a considerable degree of immunity was conferred on mice by inoculating them with the cells of tumour B, which had previously been exposed to X-rays. Strictly analogous to our findings is his observation that too long an exposure to the X-rays destroyed the immunity-conferring power of the cells.

TABLE I.

Time of Irradiation.	Number of Mice.		Testing Inoculation.	
	Inoculated.	Survived.	Positive.	Negative.
1 hour	23	17	1	16
Controls	33	27	20	7
2 hours	20	13	2	11
Controls	18	17	15	2
4 hours	12	10	2	8
Controls	16	13	7	6
6 hours	34	24	8	16
Controls	45	33	20	13
12 hours	33	22	12	10
Controls	48	37	29	8
24 hours	20	20	10	10
Controls	16	14	7	7

Percentage of "Takes."		Extent of Immunity produced.
Irradiated.	Controls.	
1 hour, 5·9 p.c.	74 p.c.	92 p.c.
2 hours, 15·4 ,,	88 ,,	82 ,,
4 ,, 20 ,,	53 ,,	62 ,,
6 ,, 33 ,,	61 ,,	46 ,,
12 ,, 54 ,,	78 ,,	31 ,,
24 ,, 50 ,,	50 ,,	0 ,,

One experiment corresponding to an exposure of six hours is not included owing to the failure of the controls, only three out of fourteen mice surviving.

In the preceding results the immunity conferred by the irradiated tumour has been tested fifteen days after its inoculation into the mice. The simultaneous inoculation of normal and irradiated pieces of tumour into the same mouse has been shown in the previous paper to lead to nearly the same percentage of "takes" as when normal tumour alone was inoculated. This is still the case when small pieces

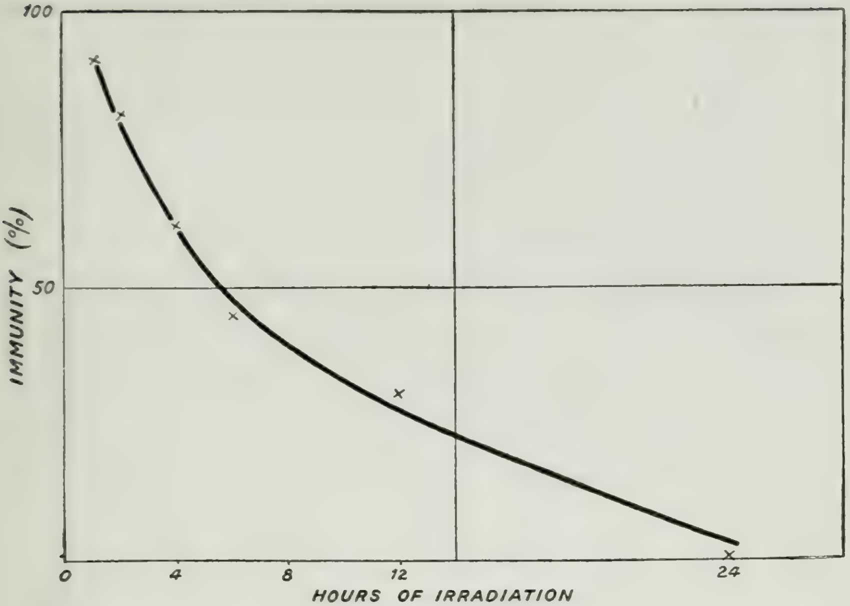


FIG. 1.

(volume about 0·005 c.c.) of normal tumour are put into the right axilla, and as much as 0·1 c.c. of irradiated material into the left axilla, as may be seen from the data in Table II.

TABLE II.

	Inoculated.	Survived.	Positive.	Negative.
Small piece in right axilla, 0·1 c.c. irradiated tumour in left axilla	12	11	10	1
Small piece in right axilla (controls)	23	21	19	2

In view of the considerable degree of immunity which this quantity (0·1 c.c.) of irradiated tumour can produce after fifteen days, this result clearly shows the importance of the time factor.

It has already been shown * that irradiated cells when injected persist in the animal for several days: that they appear to proliferate to some extent, more numerous cells being seen up to about the sixth day than in grafts removed

* Loc. cit.

at an earlier date; but that soon afterwards the cells diminish in number, so that at about the eighth day the graft consists of fibrous tissue with only a few scattered tumour cells recognisable. Similar series of grafts have since been examined in order to compare the effects of irradiation for more prolonged periods with those previously observed. Tumour tissue has been irradiated for one, six, twelve, and twenty-four hours, injected into mice simultaneously with non-irradiated tissue, and the grafts removed for investigation at intervals. Nothing definite has been observed with regard to the effect of the increase of dose, the variations in the different grafts examined being too great to allow of a satisfactory comparison; but it has been found that even after an exposure of twenty-four hours the tumour tissue behaves in a manner similar to that after comparatively short exposures, such grafts and the controls removed together on the sixth day after inoculation being so similar that they can easily be confused, the tumour cells showing mitoses and being more numerous than in grafts, irradiated or control, removed at an earlier date. This observation is contrary to what might have been anticipated from the immunising action of such irradiated tissue. In view of the lack of immunity conferred by such tissue, after an exposure of twenty-four hours, it seemed probable that the power of these tumour cells of persisting and undergoing proliferation would also be destroyed, for Haaland (1910[2]) has shown that protection is associated with the injection of living cells.

Immunity after Operation.

Several observers have recorded that in spite of careful surgical removal of well-established tumours, there is a considerable liability to recurrence; this is generally attributed to minute traces of the tumour having been left behind.

Whether the frequency of such recurrence could be diminished by the inoculation of irradiated tumour cells has been tested in the following manner: A number of mice were inoculated with small pieces of normal tumour; after about three to four weeks the growing tumours were surgically removed under ether, and on the following day the mice were inoculated subcutaneously with 0·1 c.c. of their own tumour,

after it had been irradiated just sufficiently long to ensure that it would not grow again upon inoculation. These mice were kept under observation to see whether recurrence would occur at the site of removal of the tumour. As these experiments proceeded it was seen that the reinoculated tumour material took a considerable time to be completely absorbed, and that recurrences occurred during this time.

It was felt that if some means could be found by which the absorption of this material could be accelerated, it would be an advantage. Intraperitoneal inoculations were attempted, but this method proved too fatal to continue with, for of twelve mice operated upon and treated in this way only two survived one month, one of which showed a recurrence at the fifth week after operation.

Return was therefore made to subcutaneous inoculation of the irradiated tumour, but previous to irradiation a small quantity of physiological saline was added to it, and the emulsion was kept agitated in a mechanical shaker for thirty or forty minutes, to ensure a uniform suspension. This was inoculated into the mice in two doses of 0·05 c.c. each, generally on the first and fourth days after operation, and the mice were kept under observation as before.

For purposes of comparison it is necessary to know what is the normal frequency of recurrence of the tumour after operation; and, in view of its probable dependence upon the technique of the operator, these controls have been done at intervals extending over the whole period during which this kind of experiment has been in progress.

From the collected results in Tables III., IV., and V., it will be seen that without any subsequent treatment there were recurrences in 68 per cent. of the cases: this percentage fell to 48 per cent. when the mice operated on were reinoculated with 0·1 c.c. of their own tumour after it had been irradiated, and to 24 per cent. when they were given irradiated emulsion in two separate doses of 0·05 c.c.

It will be seen from the tables that of the thirty-eight treated mice which survived one month, fourteen recurred, i.e., 37 per cent. compared with 68 per cent. in the case of untreated animals. The recurrences in the treated animals appeared at a rather later date than in the controls.

TABLE III.—*Twenty-six Mice operated on.*

Treatment	0·1 c.c. irradiated tumour				
Result....	21 survived 1 month				
	Weeks after Operation.				
	1	2	3	4	5
10 Recurrences	3	1	3	1	2

TABLE IV.—*Forty-four Mice operated on.*

Treatment	0·05 c.c. irradiated emulsion (twice)			
Result	17 survived 1 month			
	Weeks after Operation.			
	1	2	3	4
4 Recurrences	1	1	–	2

TABLE V.—*Thirty-one Mice operated on.*

No Treatment					
Result	19 survived 1 month				
	Weeks after Operation.				
	1	2	3	4	5
13 Recurrences	7	3	2	–	1

It may be questioned whether an analogous procedure to the above is justifiable in operable cases of malignant disease in human beings. Although the frequency of recurrence is reduced to about one-half, the percentage of treated animals surviving one month was 54 per cent. compared with 61 per cent. in the case of the controls. The mice cannot generally be said to appear well during the treatment, and it is possible that the reduced frequency of recurrence is in some measure due to this condition.

SUMMARY.

1. Mice are made immune to inoculation of carcinoma (Twort) by means of irradiated tumour cells.

2. Prolonged irradiation of the cells abolishes this immunity-conferring power, but does not prevent an initial proliferation on their part.

3. Some evidence is brought to show that the frequency of recurrence of this tumour after operation is diminished if the mice are reinoculated with irradiated tumour.

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[3] Wedd and Russ, "Journ. Path. and Bacteriol.," Cambridge, 1912–13, vol. xvii., p. 1.

EXPERIMENTS TO DETERMINE WHETHER VARIATIONS IN TEMPERATURE INFLUENCE THE EFFECTS PRODUCED WHEN MALIGNANT CELLS ARE IRRADIATED BY RADIUM BROMIDE.

By E. H. LEPPER.

The experiments were suggested by the marked differences that obtain between clinical findings and the results of laboratory experiments.

Morson has shown that a tube containing 100 mgr. of radium bromide inserted into a carcinomatous growth and kept there for 24 hours leads to a definite necrosis of the cells surrounding the tube.

Russ, working with mouse carcinoma and rat sarcoma, has found that irradiation of grafts for about $1\frac{1}{2}$ hours by 7 mgr. of radium bromide is sufficient to prevent their continuous growth after inoculation, but that even 24 hours radiation outside the body does not lead to any detectable histological changes.

When a tumour is radiated, *in situ*, it is possible that the circulating blood, the tissue ferments, and the body temperature play an important role in the results obtained. Russ suggested that by radiating malignant cells at 37° C., it would be possible to find out whether the body temperature is one of the factors responsible for the clinical findings.

The results are shown in Table I. Fifteen minutes radiation at 35° C. is apparently sufficient to prevent the graft

Experiments with Mouse Carcinoma.

Table I.

Source of Radiation.	Time.	Temperature.	Number of Mice Surviving. 28 days.	Positive.	40 days	Positive.	Remarks.
5 mgr. RaBr	15 min.	35° C.	6	0	5	0	—
" " "	30 "	"	8	0	5	0	—
Nil	60 "	"	7	4	6	4	Controls

Table II.

Source of Radiation.	Time.	Temperature.	Number of Mice Surviving. 21 days.	Positive.	30 days	Positive.	Remarks.
7 mgr. RaBr	30 min.	37° C.	4	3	3	2	—
Nil	—	—	4	2	3	1	Controls

taking. The control tumours in this series grew more slowly than usual, and the percentage of positive was low, so that it was thought advisable to repeat the experiment (Table II.). Here, although the number of mice surviving is small, it is seen that 30 minutes at 37° C. is not sufficient to prevent the growth of the grafts, so that the results of the first series must be put down to the condition of the tumour at the time of experiment, it was growing badly and not in a suitable condition for investigation.

Experiments with Rat Sarcoma.

The results are seen in Table III. In all cases the source of radiation was 7 milligrammes of radium bromide. Thin slices of tumour were placed between sterile sheets of mica, ringed round with cement to prevent drying, and exposed to the radium first one side and then the other for half the period of radiation.

It will be seen that the grafts radiated at 37° C. grew less well than those treated at room temperature. As the controls

Experiments with Rat Sarcoma.

Table III.

Time of Radiation.	Temperature.	No. of Rats.	Nodules, end of 8 Days.	Nodules, end of 21 Days.	Per cent. Disappearing Ultimately.	Remarks.	Control: No. of Rats.	Control: Per cent. Positive.	Control: Per cent. Disappearing Ultimately.	Control: Remarks.
1 hour 10 min.	15° C.	3	3	3	66	—	3	100	75	—
1 hour 10 min.	37·5° C.	4	3	2	75	—	1	100	50	Heated 37° C.
1 hour 20 min.	15° C.	4	3	2	100	—			—	1 hour 20 min.
1 hour 20 min.	37·5° C.	4	4	1	100	—	—		—	—

Table IV.

Time of Radiation.	Temperature.	No. of Rats.	Nodules, end of 8 Days.	Nodules, end of 21 Days.	Per cent. Disappearing Ultimately.	Remarks.	Control: No. of Rats.	Control: Per cent. Positive.	Control: Per cent. Disappearing Ultimately.	Control: Remarks.
1 hour 10 min.	37° C.	3	3	2	100	—	4	100	50	—
1 hour 10 min.	1·5° C.	3	3	3		Died end of 4 weeks	4	100	50	Heated 37° C.
1 hour 20 min.	37° C.	3	3	2	66	—	—	—	—	1 hour 20 min.
1 hour 20 min.	1·5° C.	4	3	2	33	—	—	—	—	—

Table V.

Time of Radiation.	Temperature.	No. of Rats.	Nodules, end of 8 Days.	Nodules, end of 21 Days.	Per cent. Disappearing Ultimately.	Remarks.	Control: No. of Rats.	Control: Per cent. Positive.	Control: Per cent. Disappearing Ultimately.	Control: Remarks.
1 hour ...	1·5° C.	5	5	2		Died end of 4 weeks	—			
1 hour ..	37° C.	5	5	3	40	—	4	100	25	

gave a high percentage of disappearing tumours the experiment was repeated. In this series one set of grafts was radiated at the temperature of the ice box.

The results are seen in Table IV. The grafts radiated at 1·5° C. for 1 hour 10 minutes grew better than those treated for the same time at 37° C., but all the grafts radiated for 1 hour 20 minutes grew about equally well.

An experiment in which the period of radiation was reduced to 1 hour was carried out, Table V. Here the grafts radiated at 37° C. grew distinctly better than those radiated at 4° C.

COMBINED TABLE VI.

Temperature.	Number of Rats.	Free from Nodules, end of 21 days.	Per cent	Ultimately Free.	Per cent.
CONTROLS.					
Room	11	0	0	5/11	45
37° C. for 1 hour 20 minutes	8	0	0	4/8	50
RADIATED FOR 1 HOUR 10 MINUTES AND 1 HOUR 20 MINUTES.					
37° C.	14	7	50	11/13	84
Room	7	1	14	6/7	85
Cold	7	2	28	2/4	50

In order to obtain a clearer view of the entire series of experiments on rat sarcoma, Tables III., IV., and V. have been combined in Table VI., and the actual size of the tumours obtained graphically, represented in Figs. 1 to 5, from which can be seen :—

1. The differences in percentage of takes and rate of growth between the control and radiated grafts (cf. Figs. 1 and 2 with 3, 4 and 5).

2. That heating grafts at 37° C. for 1 hour 20 minutes has no effect on their rate of growth (cf. Fig. 1 with Fig. 2).

3. That grafts radiated at 37° C. grow rather more slowly and disappear sooner than grafts which have been radiated in the cold (cf. Figs. 3 and 5).

4. That very little difference can be detected between the behaviour of grafts radiated at room temperature (15° C.) and those treated at 37° C. (cf. Figs. 3 and 4), so that in experimental work on rat sarcoma with radium the ordinary variation in room temperature need not be taken into consideration.

Fig I

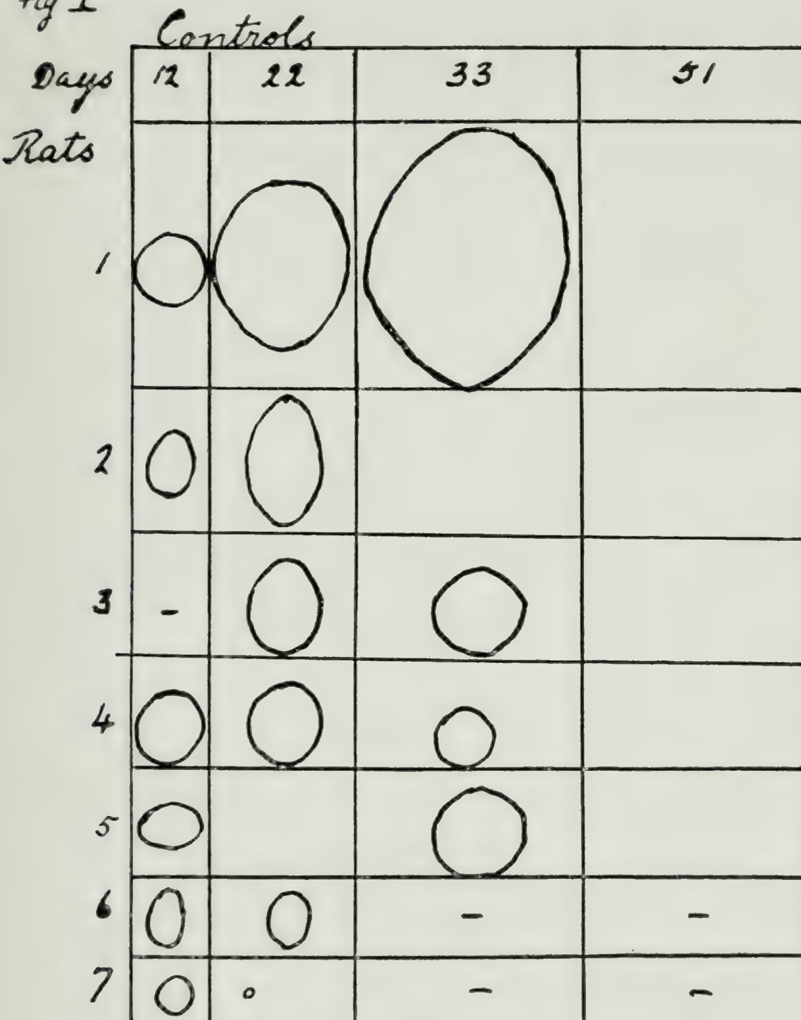


Fig II Controls
Heated at 37°C for 1 hour 20 minutes

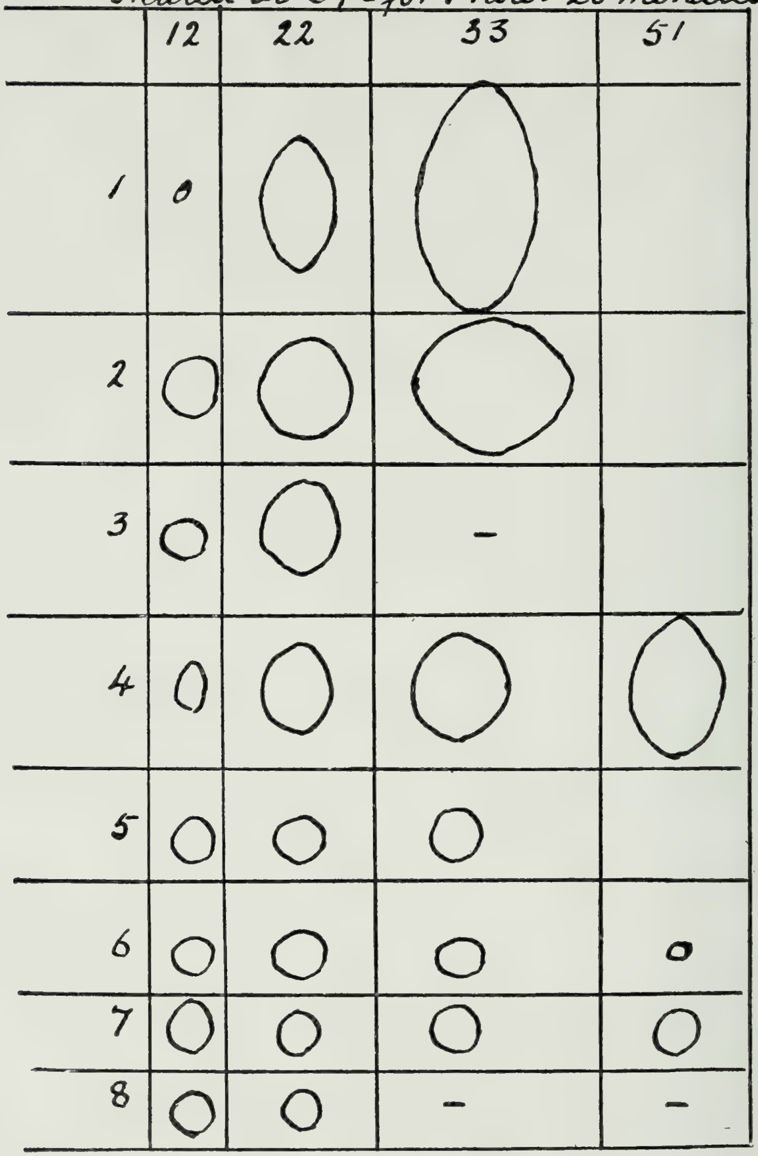
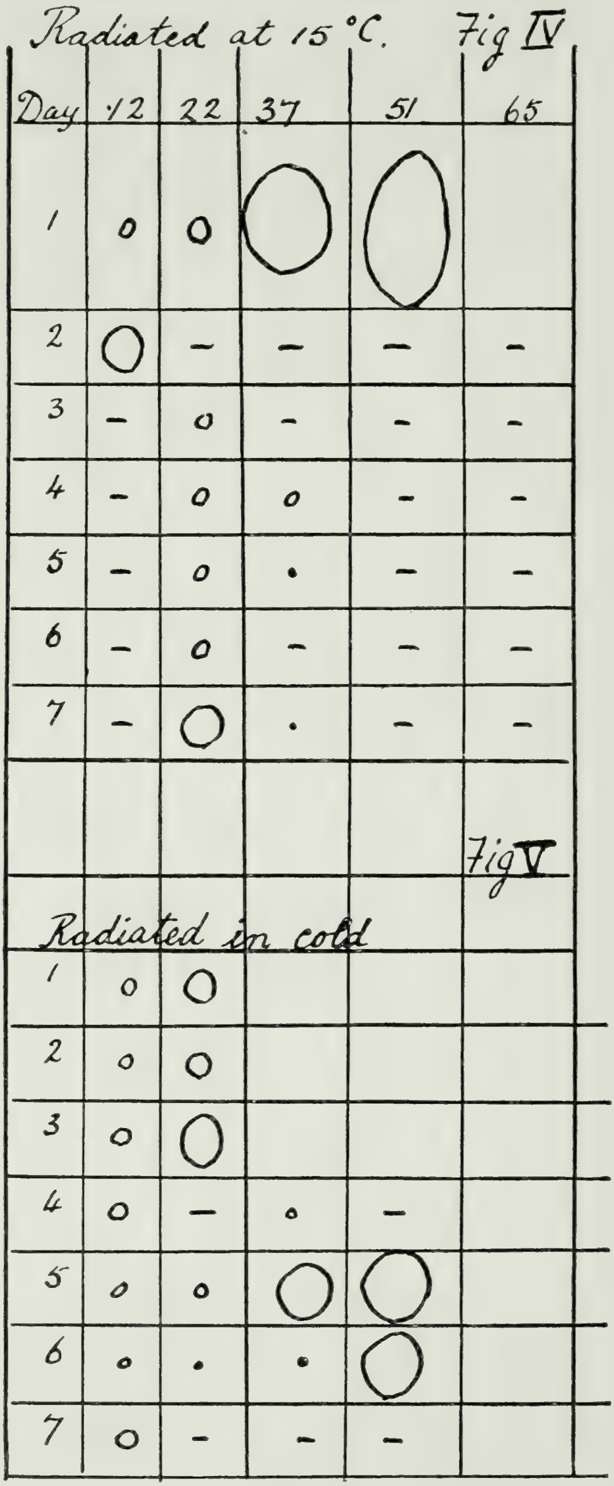


Fig III

Radiated at 37°C

Days	12	22	37	51	65
Rat 1	–	o	o	O	O
2	–	o	–	–	–
3	o	o	–	–	–
4	–	–	–	–	–
5	o	o	–	–	
6	o	–	–	–	
7	–	o	–	–	–
8	–	–	–	–	–
9	O	–	–	–	–
10	–	–	–	–	–
11	O	–	–	–	
12	–	O	O	O	
13	o	O	O		



Radiated at 15 °C.
Fig IV
Day
·12
22
37
51
65
1
2
3
4
5
6
7
Fig V
Radiated in cold
1
2
3
4
5
6
7

AN ATTEMPT TO INDUCE IMMUNITY AGAINST CANCER IN ANIMALS BY MEANS OF HEAT.

By E. H. LEPPER.

The object of the experiments was to determine whether cancerous material heated to a sub-lethal point is capable of conferring immunity.

The tumour employed was mouse carcinoma ("Twort" strain).

The Method of Heating the Tumour Material.

Glass bulbs 2 cm. in diameter were blown at the ends of glass tubing 8 mm. in diameter. These were sterilised, and thin slices or an emulsion of the tumour were placed in the bulb, and the tube sealed up and put in a bath at the required temperature.

It was found by means of a thermo-electric couple that the contents of such bulbs reached the temperature of the surrounding bath in from $2\frac{1}{2}$ to 3 minutes; they were within one degree in $1\frac{1}{2}$ minutes.

The most convenient heating apparatus proved to be a copper air bath, heated by gas, having a mercury regulator and containing a shallow glass dish of water in which the bulbs were placed. The bath had a cover made of lead, through a small opening in which a thermometer reached the water. The bath was kept at the required temperature by arranging that the temperature of the air in the cupboard was a few degrees higher than that of the water. The temperature of the bottom of the bath where the bulbs rested was that given by the thermometer.

If several bulbs were heated together the temperature of the bath fell slightly when they were put into the water; generally the variation between the extremes of temperature

did not exceed ·5° C. The mean of the highest and lowest temperature during an experiment was taken to be the temperature at which that experiment was carried out.

Preliminary experiments were made to determine the temperature to be regarded as "sub-lethal" and to be used for preparing the (hypothetical) immunising tumour material. The aim in view was to find the temperature at which heating for an hour was sufficient to prevent growth, as the longer the period of incubation the greater the risk of sepsis. On the other hand, it was not desirable to employ very short periods of exposure to heat, as the working margin between cells sufficiently damaged not to grow continuously, and yet be capable of producing immunity, and those killed outright might be so small that an immunising effect might be overlooked.

The results of heating grafts at varying temperature for varying periods of time are seen in Table I. It was found

Table I.

Temperature.	Time.	No. of Mice.	Per cent. positive in 4 weeks.	Controls. Per cent. positive.	Remark.
37° C.	4 hours	10	50	25	—
40·8° C.	45 mins.	18	50	75	—
42·25° C.	1 hour	7	25	62	—
43·3° C.	15 mins.	8	37	100	7 weeks 63% positive
43·4° C.	30 „	5	80	—	—
43·25° C.	45 „	3	0	75	—
43·3° C.	1 hour	8	0	100	—
44·3° C.	15 mins.	6	66	87	—
44·3° C.	45 „	6	0	87	—
44·75° C.	15 „	5	0	100	—
44·75°	1 hour	7	0	85	—

that heating grafts at 43·3° C for one hour prevents their subsequent growth, but that the same temperature for half an hour has very little effect on the percentage of "takes," though the appearance of the tumours is slightly delayed and the rate of growth somewhat slower than the controls.

The Immunising Power of Heated Tumour Material.

The results of treating mice with heated tumour material are seen in Table II. The percentage of "takes" in mice

TABLE II.

Temp.	Time.	Average Weight.	Heated Emulsion.	Test Inoculation.	End of 3 weeks. No.	End of 3 weeks. Per cent. positive.	End of 4 weeks. No.	End of 4 weeks. Per cent. positive.	Controls. Per cent. positive. 3 wks.	Controls. Per cent. positive. 4 wks.
44·3° C.	45 mins.	—	·1 c.c.	9 days later	5	60	5	80	87	87
44·3° C.	2¼ hrs.	—	·1 ,,	9 ,, ,,	4	25	4	50	87	87
43·4° C.	1½ ,,	17·7 grm.	·1 ,,	9 ,, ,,	9	33	3	75	85	85
43·4° C.	4½ ,,	15·4 ,,	·1 ,,	9 ,, ,,	5	20	4	50	85	85
43·25° C.	1½ ,,	13·4 ,,	·1 ,,	14 ,, ,,	6	15	3	33	54	66
43·5° C.	45 mins.	14 ,,	·1 ,,	13 ,, ,,	3	0	2	0	41	41
43·5° C.	45 ,,	16·6 ,,	·05 ,,	13 ,, ,,	8	62	5	80	41	41

which received ·1 c.c. 9 to 14 days before the test inoculation is slightly lower than in the controls, and the appearance of the tumours is somewhat delayed.

The high mortality among the mice, due to a laboratory epidemic, renders the numbers too small to draw definite conclusions, but so far as they go they are in favour of some slight degree of immunity being produced by the heated tumour cells. There was no evidence that the mice were rendered more susceptible to inoculation.

It will be noticed, however, that the percentage of "takes" in the control mice was rather low in the later experiments; and this, taken with the fact that mice treated with heated material do not seem well during the second week after injection at the time when the test inoculation is made, may be the explanation of the results obtained.

For these reasons the mouse carcinoma was given up and similar experiments were carried out with rat sarcoma. The results obtained are shown in Tables III. (determination of

TABLE III.

Temperature.	Time.	No. of Rats.	Per cent. positive. 4 weeks.	Controls. Per cent. positive.
43·3° C.	30 minutes	5	100	100
43° C.	52 ,,	5	40	100
43·3° C.	1 hour	5	0	100
43° C.	1¼ hours	3	0	100
43·3° C.	2½ ,,	5	0	100

TABLE IV.

Temp.	Time.	Heated Emulsion.	Test Inoculation.	End of 4 weeks. No.	End of 4 weeks. Per cent. positive.	Controls. Per cent. positive.
43° C.	1½ hrs.	·1 c.c.	19 days after first	3	100	100
43° C.	1½ ,,	·1 c.c. 7 days after first	12 days after second	—	—	—
43·25° C.	1½ ,,	·1 c.c.	14 days after first	—	—	—
43·25° C.	1½ ,,	·1 c.c. 5 days after first	9 days after second	5	100	100
43·25° C.	1½ ,,	·1 c.c	12 days later	5	100	100

lethal time-period at 43° C.) and IV. The injection of heated rat sarcoma did not lead to the production of any immunity to sarcoma in the rats so treated; on the contrary, rats which had received two injections of ·1 c.c. of heated emulsion bore larger tumours than the control rats.

THE IMMUNITY TO RAT SARCOMA PRODUCED IN RATS BY GRAFTS OF SARCOMA WHICH HAVE BEEN IRRADIATED BY RADIUM.

By E. H. LEPPER.

In the course of some experiments to test the effect of radiating grafts of rat sarcoma at various temperatures a number of rats were inoculated with small pieces of tumour which had been irradiated by a 7 milligramme capsule of radium bromide for periods varying from 1 hour to 1 hour 20 minutes. These rats were subsequently reinoculated with small pieces of sarcoma to see if any difference could be detected in their behaviour. It was found that only a few of the rats developed progressively growing tumours, a number showed small nodules which afterwards disappeared, and about half were negative to the test inoculation.

Table I.

Preliminary Treatment.	Positive.	Negative.	Disappearing Nodules.	Day of Test.	Positive.	ive.	Disappearing Nodules.	Controls Positive. Per cent.
Radiated 1 hr. to 1 hr. 20 min. ...	6	5	21 (9 × 9 mm.)	29 to 61	3	13	5 (1·2 × 1·3 cm.)	100
Controls	14	0	10 (25 × 21 mm.)	31 to 70	0	5	1	100

The details of the number of rats which were positive, negative, or showed disappearing tumours are given in Table I. together with the measurements of the largest tumour in each case which ultimately disappeared; these are inserted as the tumour is one which may absorb in as many as 50 per cent. of the cases.

Only those rats which were negative or in which nodules had completely disappeared were reinoculated.

It will be seen that only 3 of the 21 surviving rats (14 per cent.) gave progressively growing tumours, 5 (23 per cent.) showed small tumours which absorbed, 13 (61 per cent.) were negative. The surviving controls gave 100 per cent. of "takes"; half of these tumours subsequently disappeared.

In all cases the nodules occurring in the rats injected with radiated tumour were smaller than those found in the controls; the largest measured 9×9 mm. There was no doubt that the cells had been adversely affected by the radiation, but, as seen by the results of subsequent inoculation, not damaged so much as to abolish their power of producing an immunity towards rat sarcoma in a certain number of the rats.

TABLE II.

Preliminary Treatment.	Positive.	Negative.	Disappearing Nodules.	Day of Test.	Positive.	Negative.	Disappearing Nodules.	Controls Positive. Per cent.
Radiated 1 h. 20 m.	2	0	14 (6 × 7 mm.)	29	3	6	4 (1·2 × 1·3 cm.)	100
" 1 h.	1	0	3 (8 × 8 mm.)	40	0	2	1 (10 × 10 mm.)	100
" 1 h. 20 m.	3	5	4 (9 × 9 mm.)	61	0	5	0	100

In Table II. the rats have been grouped according to the length of time between the original injection and the test inoculation. The immunity appears to be more marked at the end of 61 days than it was at the end of 29 days. Further work on this point is now being conducted.

ON RETARDATION OF ELECTROSCOPIC LEAK FOLLOWING ESTIMATION OF RADIUM EMANATION OF THE ORDER 10^{-7} MILLI-CURIE.

By W. S. LAZARUS-BARLOW.

In 1906 and 1907 (Arch. Middlesex Hospital, Fifth and Sixth Cancer Reports) I published experiments from which I concluded that a metal disc placed in proximity to uranium, thorium, or pitch-blende for 48 hours acquires the property of retarding electroscopic leak. I further concluded that this retardation reached a maximum on the fourth to fifth day after removal of the metal from proximity with the radio-active substance, and that a return to normal rate of leak occurred after a somewhat prolonged period.

These experiments were regarded as unsatisfactory and the conclusions as erroneous, but since I observed apparent examples of the same phenomenon from time to time while working with the emanation electroscope during 1911, 1912, and 1913, I determined to re-investigate the question under improved conditions.

The present experiments were conducted in the following way: The rate of natural leak having been observed for several days, the electroscope was filled with the gases (at equilibrium value) boiled off a solution of pure radium bromide (Rutherford's or Ramsay's standard solution) having a strength of the order 10^{-7} mgr. Ra. After the emanation had remained within the electroscope for a period varying in different experiments from 3 to 48 hours the electroscope was exhausted three times in succession to 1–2 cm., and the rate of leak was observed on this and successive days. On the fourth or some subsequent day the process was repeated with

a similar Ra solution of similar strength, the object being to produce, if possible, a cumulative effect.

Charging was carried out by means of the negative terminal from storage cells, a water resistance being introduced, and the positive terminal, as well as the electroscope, being earthed. Fifty-four cells were used throughout for charging, and the telemicroscope was arranged so that the deflection (about $22\frac{1}{2}°$) corresponded to 51 on the scale, while the terminal was in contact with the upright carrying the gold leaf. Except for (1) the two days every three weeks during which the cells were being charged, and (2) during the actual observations, the gold-leaf system was kept at this constant potential over the whole period of the investigation, while the gold leaf was never allowed to fall more than the five divisions (50–45) over which the leak was uniformly taken (see, however, note, p. 99). This fall over five divisions represented closely a fall in potential of 10 volts.

Experiments were made to determine what length of charging was necessary in order to obtain reliable readings. As is shown by the following series the natural leak is appreciably slower if the gold-leaf system has been charged all night than if it has been charged only 30 seconds immediately after the first and subsequent estimations of leak. This is true, even though the leaf have not been allowed to fall below the five divisions on the scale over which the leak is taken on each occasion :—

					Min.	Sec.
10.3 a.m.	1st observation	50th to	45th	division	70	17
11.16 ,,	2nd	,,	,,	,,	66	47
12.24 p.m.	3rd	,,	,,	,,	63	8
1.30 ,,	4th	,,	,,	,,	65	51
2.45 ,,	5th	,,	,,	,,	69	16
3.57 ,,	6th	,,	,,	,,	61	45

If, however, a period of three hours be allowed for recharging after an observation has been taken, the second reading differs from the first by an amount not exceeding about 3 per cent. This is seen by the following series of six occasions upon which a second determination of the leak was made after allowing the gold-leaf system to be recharged for

a period of 3 hours from the time when the first determination was ended :—

		First Determination.			Second Determination.	
		Min.	Sec.		Min.	Sec.
Oct. 29	...	72	37	...	71	45
Nov. 6	...	78	40	...	79	22
,, 14	...	86	2	...	85	47
,, 26	...	77	21	...	76	48
Dec. 3	...	101	29	...	98	18
,, 4	...	97	56	...	96	7

For the actual investigation, therefore, the first determination of leak after an all-night charging has been taken, and in those experiments* in which a second determination of leak has been necessary (Series II B), a period of three hours' recharging at constant potential was allowed to intervene between the end of the first determination and the commencement of the second. This period of three hours does not include the length of time taken by the leaf to reach the 50th division from the point it has assumed on the scale when the charging terminal has been removed and the cap has been replaced on the upper part of the electroscope.

Actual charging was carried out by a simple device. The negative terminal from the storage cells, after passing the water resistance, was soldered to a looped length of platinum foil ($1\frac{1}{4}$ inch × $\frac{1}{8}$ inch), the other end of which was soldered to about 2 inches of platinum-iridium wire. This wire, close to its union with the platinum foil, was fixed by sealing-wax to the lower end of the stopper of an ordinary two-way glass tap. The whole was fixed on a wooden stand, and it was possible to swing the charging rod through a horizontal arc by turning the tap whenever it was desired to recharge or disconnect. The standard carrying the golf leaf terminated in a short length of platinum foil coiled in such a way as to ensure a good contact when charging. Entry of dust into the electroscope during charging was avoided as far as possible by means of two superposed cardboard boxes with appropriate slits for the charging terminal. The air of the room was kept dry and at a temperature varying a few degrees on either side of 18° C. by means of a small gas stove which burnt day and night.

* See footnote, p. 99.

Experiments.

Series I.—Experiments showing the absence of retardation in electroscopic leak as the result of manipulations necessary for observations with the emanation electroscope when no radium is present. (Blank experiments).

The following series of N.L. values was obtained by Beckton under my supervision (in the course of an investigation upon herrings, published in Arch. Middlesex Hospital, Twelfth Cancer Report, 1913, p. 146) by means of the same electroscope as was used in the present investigation. It indicates that in the absence of radium the manipulations necessary for making observations with the emanation electroscope are not followed by retardation of leak.*

Date.	N.L. in div./min.	Mean N.L. in div./min.	Remarks.
18/12/12	·070		
19/12/12	·067		2 estimations made ; no radium found.
20/12/12	·068	·071	1 ,, ,, ,, ,,
23/12/12	·080		1 ,, ,, ,, ,,
24/12/12	·070		
30/12/12	·070		
31/12/12	·059		
1/1/13	·071	·068	1 estimation made ; no radium found.
2/1/13	·064		1 ,, ,, ,, ,,
3/1/13	·074		
4/1/13	·071		
6/1/13	·076		2 estimations made ; no radium found.
7/1/13	·073	·072	1 ,, ,, ,, ,,
8/1/13	·064		1 ,, ,, ,, ,,
9/1/13	·077		2 ,, ,, ,, ,,
10/1/13	·071		2 ,, ,, ,, ,,
13/1/13	·081		2 ,, ,, ,, ,,
14/1/13	·070	·074	2 ,, ,, ,, ,,
15/1/13	·077		1 ,, ,, ,, ,,
16/1/13	·069		

* For Beckton's investigations the leaf was kept charged during the intervals of experiment, though not at a constant potential, being brought to the required starting point for an observation by means of a Phillips charger. The series was carried out at the same time of the year as the experiments shown in Figs. 1–4, but is not comparable with them in order of magnitude, since the insulation broke down, and was repaired August to September 1913. However, between December 12, 1912 and February 5, 1913, 82 estimations of natural leak at atmospheric pressure were made with this instrument, the mean being ·085 div./min., the absolute minimum being ·058 div./min., and all but eight observations being ·070 div./min. or upwards. The mean of the first half of the observations was ·077, of the second half was ·093 div./min.

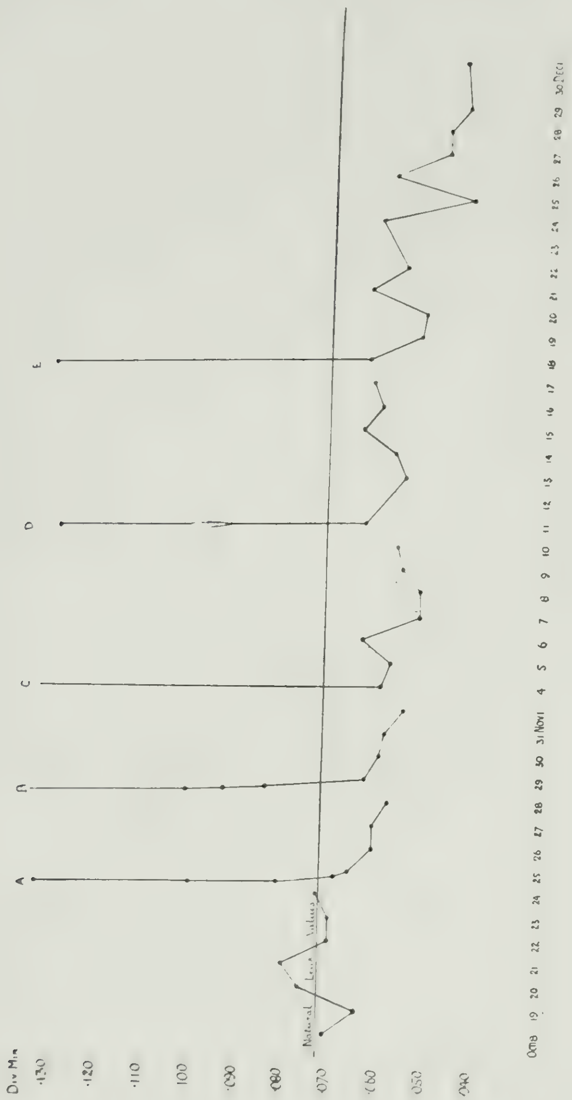

Div Min
·130
·120
·110
·100
·090
·080
·070
·060
·050
·040
A
B
C
D
E
Natural Leak Values

FIG. 1.

Series II.—Experiments showing the retardation of electroscopic leak which follows on decay of active deposit derived from radium emanation of the order 10^{-7} *millicurie.*

(a) Air Unchanged in Electroscope after Removal of Emanation. Leak at Atmospheric Pressure.

These experiments were five in number, and are graphically presented in Fig. 1, the condensed protocols being given at the end of the paper. In Fig. 1 it is to be noted that the observations on natural leak, taken daily for a week prior to introduction of any emanation into the electroscope, varied to a small degree above and below the mean level of ·072 divisions per minute. From October 24th, however, to the end of this part of the investigation (December 1st) the level of the observations slopes downwards, while (with the exception of the experiment, November 11th to 17th) the absolute lowest leak obtained in any experiment is lower than that

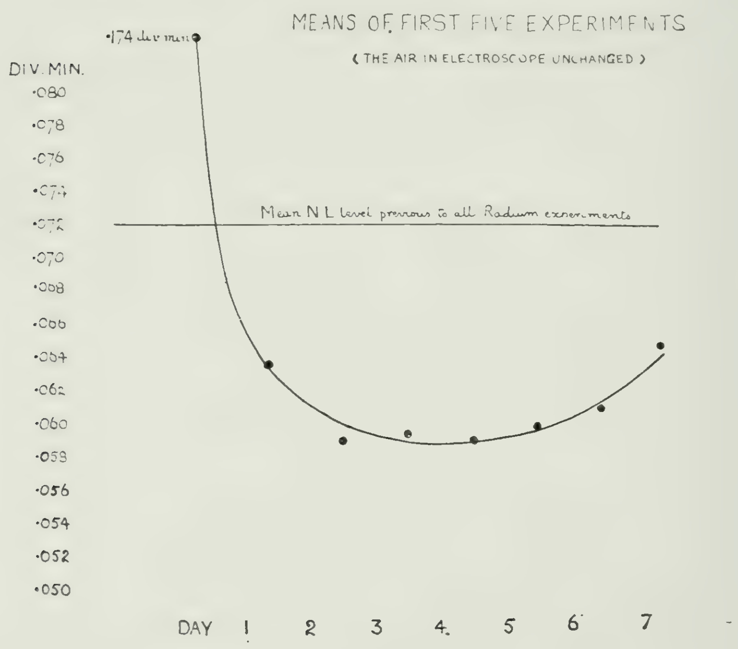


FIG. 2.

obtained in any of the previous experiments, so that the leak at the end of November was about ·045 division per minute.

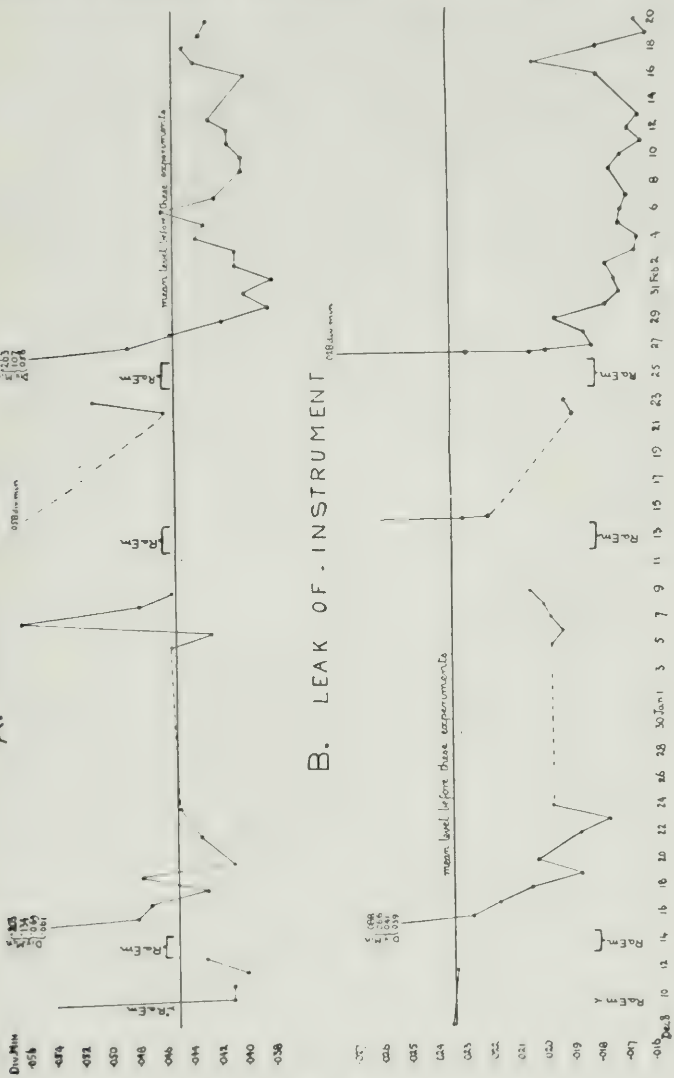


FIG. 3.

In Fig. 2 the different values obtained on the first seven days of the five experiments are reduced to means and presented graphically. It is seen that a curve is produced with

the lowest point on the fourth to fifth day, by which time the leak is about 20 per cent. lower than it was prior to the introduction of radium emanation into the electroscope. Comparison of this curve and that in Fig. 5 (which gives the means of the entire series of eleven experiments made during the investigation without selection) shows their close general resemblance.

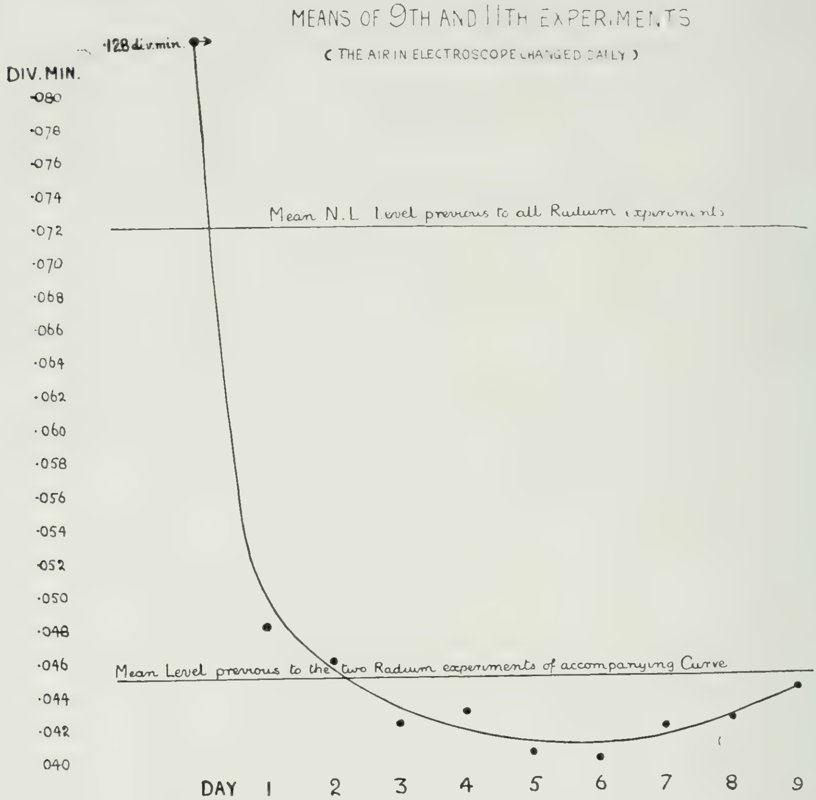


FIG. 4A.

(b) Air in Electroscope Changed Daily after Removal of Emanation. Portion of Total Leak due to Instrument.

Partly because it was possible that the fall in leak observed during the first four days after decay of active deposit might be explained by decay of such emanation as was contained in the air with which the electroscope was

filled on the first day, and partly because it was desirable to determine the portion of leak due to the instrument, in three experiments leak was determined (1) at atmospheric, (2) at diminished pressure. One of the experiments failed in part owing to defective insulation (cf. Fig. 3, January 16th to 21st, and protocol at end of paper), the remaining two were used to obtain observations over a period of about three weeks after removing emanation from the electroscope by three successive exhaustions. The emanation from $2 \cdot 5 \times 10^{-7}$ mgr. Ra at equilibrium value was allowed to remain in the electroscope for 44, 44, and 48 hours respectively in the three experiments. The method of experiment was as follows:—The leak at atmospheric pressure having been determined, the gold-leaf system was recharged at constant potential, and the electroscope was exhausted to 1–2 cm. pressure. After three hours' recharging * the leak was taken at this diminished pressure, at the end of which the leaf was recharged for the night. Next morning air was allowed to enter the electroscope gradually, and the leak was taken when atmospheric pressure had been regained. In this way the air and the residual air within the electroscope for the necessary pair of determinations of leak differed to the least

* Owing to the fact that the entire period occupied in obtaining the necessary (1) leak at atmospheric pressure (2) leak at 1–2 cm. pressure over 5 divisions on the scale amounted to about 11 hours, observations were made to see the differences introduced by taking (*a*) the leak in both instances over 3 divisions only, or (*b*) leak at atmospheric pressure over 3 divisions, leak at diminished pressure over 5 divisions, or (*c*) in both instances over 5 divisions, as in the previous experiments of the investigation. The following values were obtained :—

	Portion of Total Leak at Atmospheric Pressure due to	
	Air.	Instrument.
Leak taken on 3 divisions at atmospheric, 3 divisions at diminished pressure	·0321 div./min.	·0254 div./min.
Leak taken on 5 divisions at atmospheric, 5 divisions at diminished pressure	·0350 ,,	·0227 ,,
Leak taken on 3 divisions at atmospheric, 5 divisions at diminished pressure	·0353 ,,	·0222 ,,

It was further found that if the first estimation of leak only extended over 3 divisions, reliable readings could be obtained with two hours' recharging instead of three. In the last experiment, therefore (January 24th onwards), the leak at atmospheric pressure was determined on 3 divisions, and the electroscope was recharged for 2 hours. In this way a saving of nearly 2 hours was made on the pair of observations at a negligible cost in accuracy of the results. Leak at diminished pressure was determined on 5 divisions, as in all other cases.

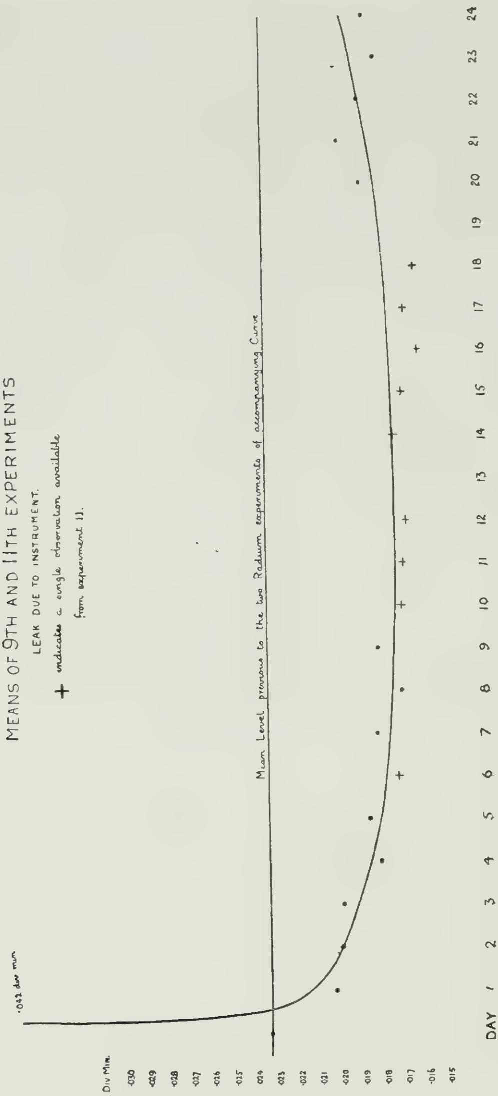


FIG. 4B.

degree from one another in percentage composition by reason of atmospheric variations in content of emanation. A simple calculation from the two values thus obtained rendered possible a determination of the amount of the total leak at atmospheric pressure which was due to the instrument. The

values thus obtained are not quite accurate, since that part of the gold-leaf system contained in the upper compartment of the electroscope was not under diminished pressure conditions when the electroscope was exhausted.

In Fig. 3B the values obtained in this way for the leak due to instrument are represented graphically. A general similarity is obvious between the curves afforded by the instrument leak in the experiments beginning December 13 and January 24 (and that beginning January 12 so far as it is reliable), as well as a similarity between the instrument leak in these experiments and the curves afforded by the total leak at atmospheric pressure in these and the other experiments of the investigation (cf. Figs. 1 and 3A, also Figs. 2, 4A, 5).

In Fig. 4B is given the composite curve of the "instrument values" of the experiments beginning December 13 and January 24, Fig. 4A being the composite curve of the total leak at atmospheric pressure in the same experiments for the first nine days.

Similar evidence of a reduction in the rate of leak due to the instrument is seen in certain values obtained prior to this part of the research. Thus reference to the protocols at the end shows that on March 26th, 1913, the instrument leak was ·045 div./min., that after four radium estimations it was ·037, and that after a month's rest it was ·046. Similarly, on November 28th the instrument leak was ·031 div./min., and on December 8th, after two radium estimations, it had fallen to ·024 div./min.

Series III.—Experiment showing the failure to find a retardation of electroscopic leak following on the decay of active deposit derived from radium emanation of the order 15 *milli-curie.*

In view of the cumulative effect which is apparent in the previous experiments it was thought possible that with the use of large quantities of emanation a retardation might occur which would be demonstrable with ease. As is seen by the following experiment this event did not obtain. On the contrary an increasing acceleration of leak (presumably due to

the formation of RaE and RaF) manifested itself over the period of five weeks, during which observations were made. A platinum wire 1 inch in length was made the negative pole of a small circuit in 15 milli-curies for a period of 12 days. At the end of the same day of removal from the emanation the leak due to the platinum wire, in an alpha ray electroscope of constant capacity (Arch. Middlesex Hospital, Eleventh Cancer Report, 1912, p. 80), was 1·54 div./min. Next day the wire caused a leak of ·455 div./min. Subsequent readings during the first two weeks gave mean values as below :—

1st week	...	·486 div./min.
2nd ,,	...	·689 ,,

On the 14th day the reading was ·843 div./min., and with the idea that emanation might be occluded, the platinum wire was momentarily raised to redness in the flame. The leak immediately fell to ·225 div./min., and the mean readings for the succeeding weeks were :—

3rd week	...	·234 div./min.
4th ,,	...	·301 ,,
5th ,,	...	·380 ,,

At no time, therefore, was any evidence of retardation discernible.*

Summary.

From the preceding sections it is seen that there is substantial agreement amongst the various experiments constituting the research. If all the values obtained in the investigation for leak at atmospheric pressure be tabled according to the day after removal of emanation on which they were observed a composite curve can be drawn. This has been done in Fig. 5 (no value being excluded even though it be probable that it is erroneous, e.g., values of January 15th to 21st, 1914) for the day during which decay of active deposit was taking place, and seven days subsequently. It will be

* A similar difference between the action of small and of large quantities of radium was found by Beckton and myself to obtain in the case of the ova of Ascaris megalocephala (Arch. Middlesex Hospital, Twelfth Cancer Report, 1913, p. 17). We found that whereas exposure of the ova to the alpha, beta, and gamma radiations of radium in quantities of the order 5×10^{-7} mgr. for 30 hours accelerates the rate of subsequent division, exposure to greater quantities or for longer periods progressively retards the rate of subsequent division.

recognised from inspection of the following table, from which Fig. 5 is drawn up, that the means for the first four days are based on the entire series of eleven experiments, and are therefore more satisfactory than those for the last three days:—

Experiment.	Leak During Decay of Active Deposit.	Leak on Days after Decay of Active Deposit.						
		Day 1.	Day 2.	Day 3.	Day 4.	Day 5.	Day 6.	Day 7.
	Div. Min.	Div. Min.	Div./Min.	Div./Min.	Div./Min.	Div./Min.	Div./Min.	Div./Min.
I.	·137 ·100 ·081 ·069	·066	·061	·061	·058	—	—	—
II.	·101 ·093 ·084	·063	·060	·059	·055	—	—	—
III.	—	·060	·058	·064	·052	·052	·056	·057
IV.	·405 ·310 ·225 ·147 ·072	·064	·060	·056	·058	·064	·061	·063
V.	·262 ·069	·064	·053	·052	·064	·057	—	·066
VI.	—	·044	·049	·051	·053	—	—	—
VII.	—	·087	·084	·079	·046	—	—	—
VIII.	—	·041	·041	·040	·043	—	—	—
IX.	·203 ·134 ·069 ·061	·048	·043	·043	·048	·041	—	·043
X.	·058 ·058	075	·068	·063	·066	·072	·067	·089
XI.	·263 ·107 ·056	·048	·045	·042	·038	·040	·038	·041
Means	·1376	·0600	·0565	·0555	·0528	·0543	·0555	·0598

In comparing this composite curve of all experiments with Fig. 2, a composite curve of the first five experiments and Fig. 4A, a composite curve for the ninth and eleventh experiments beginning, respectively, December 13 and January 24, it is seen that although a general similarity in shape of the three curves is recognisable yet there are certain differences. These are best determined by comparing Figs. 2 and 4A. In the curve from early experiments, the lowest portion is on the fourth day, is 10 per cent. lower than it was on the first day, and 20 per cent. lower than the mean level of

natural leak prior to the introduction of radium emanation into the electroscope. In the curve from late experiments, on the other hand, the lowest portion is on the fifth to sixth day, is 18 per cent. lower than it was on the first day, and 40 per cent. lower than the mean level of natural leak prior to the introduction of radium emanation into the electroscope. This evidence for a cumulative effect is supported by the behaviour of the later parts of the two curves, the curve

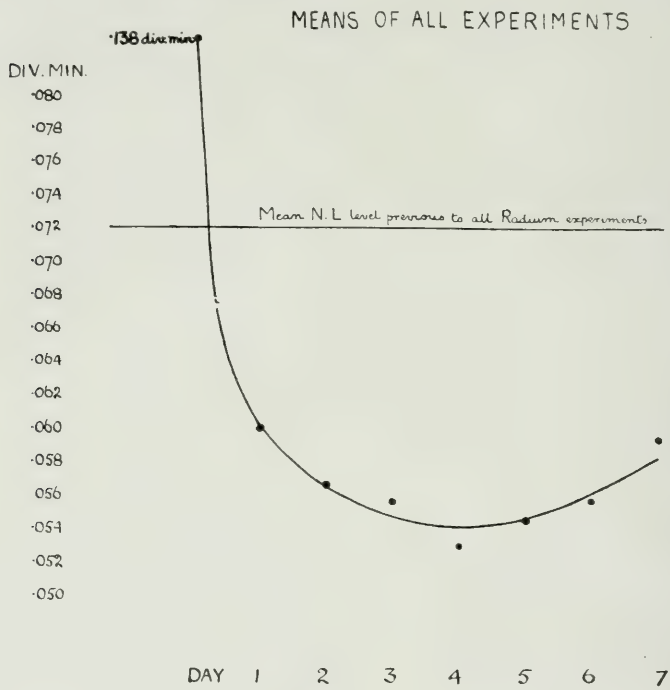


Fig. 5.

from early experiments rising 8 per cent. in three days, while the curve from late experiments rises 7 per cent. in three to four days.

From the daily determinations of the portion of leak due to instrument it is seen that after it had contained radium emanation a diminution was manifested in the leak for which the instrument could be held accountable. This diminution was progressive, and set in with comparative rapidity, but recovery was slow. Thus examination of the curve in

Fig. 4B shows that by the 12th to 13th day, when the minimum was reached, leak had fallen from ·0217 div./min. on the first day to ·0173 div./min. (20 per cent.), whereas from this time till the 24th day the rise was from ·0175 to ·0195 div./min. (11 per cent).

It thus appears from the entire investigation that, subsequent to the decay of active deposit derived from radium emanation of the order 10^{-7} milli-curie, electroscopic leak shows a progressive retardation followed by a recovery which is slower than the initial fall in rate of leak. This retardation is associated with a progressive diminution in the portion of the total leak which is referrible to the instrument, and, similarly, the recovery from a retarded condition that obtains in the case of the total leak is associated with a progressive recovery on the part of the leak due to instrument. Hence a general similarity obtains between the curve described by plotting out the values ascribable to the instrument and the curve given by values obtained for instrument and air at atmospheric pressure. No such retardation of leak was found in the case of blank experiments, nor was retardation found after the decay of active deposit from 15 milli-curies for 12 days upon a platinum wire. In the latter instance there was observed by the alpha ray electroscope a progressive increase of leak due to the formation of RaE and RaF after the active deposit upon the wire had decayed.

Condensed Protocols of Experiments in Series II A.

Date.	Leak div./min	Air Pressure mm. Hg.	Remarks.
18/10/13	·070	—	Natural leak observations.
19/10/13	·064	—	
20/10/13	·076	—	
21/10/13	·080	749	
22/10/13	·070	755	
23/10/13	·070	764	
24/10/13	·073	768	
			Emanation of $1·57 \times 10^{-7}$ mgr. Ra (equilibrium) introduced into electroscope for 3 hours.
	(*a*) ·137		Decay of active deposit after three successive exhaustions.
	(*b*) ·100		
	(*c*) ·081	—	
	(*d*) ·069	—	

CONDENSED PROTOCOLS OF EXPERIMENTS IN SERIES II A.—*continued.*

Date.	Leak div. min.	Air Pressure mm. Hg.	Remarks.
25/10/13	·066	763	
26/10/13	·061	752	
27/10/13	·061	751	
28/10/13	·058	747	
			Emanation of 7×10^{-7} mgr. Ra (equilibrium) introduced into electroscope for 3 hours.
	(*a*) ·101	—	Decay of active deposit after three successive exhaustions.
	(*b*) ·093	—	
	(*c*) ·084	—	
29/10/13	·063	742	
30/10/13	·060	750	
31/10/13	·059	758	
1/11/13	·055	—	
3/11/13			Emanation of 7×10^{-7} mgr. Ra (equilibrium) introduced into electroscope for 3 hours.
4/11/13	·060	761	
5/11/13	·058	751	
6/11/13	·064	747	
7/11/13	·052	751	
8/11/13	·052	750	
9/11/13	·056	754	
10/11/13	·057	753	
			Emanation of 7×10^{-7} mgr. Ra (equilibrium) introduced into electroscope for 3 hours.
	(*a*) ·405	—	Decay of active deposit after three successive exhaustions.
	(*b*) ·310	—	
	(*c*) ·225	—	
	(*d*) ·147	-	
	(*e*) ·072	—	
11/11/13	·064	749	
12/11/13	·060	744	
13/11/13	·056	743	
14/11/13	·058	744	
15/11/13	·064	752	
16/11/13	·061	762	
17/11/13	·063	764	
			Emanation of 7×10^{-7} mgr. Ra (equilibrium) introduced into electroscope for 3 hours.
	(*a*) ·262	—	Decay of active deposit after three successive exhaustions.
	(*b*) ·069	—	
18/11/13	·064	763	
19/11/13	·053	771	
20/11/13	·052	765	
21/11/13	·064	756	
22/11/13	·057	—	
24/11/13	·066	764	
25/11/13	·043	768	
26/11/13	·065	769	
27/11/13	·048	772	
28/11/13	·048	772	
29/11/13	·044	771	
1/12/13	·045	765	

Condensed Protocols of Experiments in Series II B.

Date.	Leak. div. min.	Air Pressure, mm. Hg	Leak at Atmospheric Pressure due to— Air.	Instrument.	Remarks.
26/3/13	·085 ·046	755 19½	·040	·045	
27/3/13	·097	752	—	—	Ra estimation made (9×10^{-8} mgr. Ra)
28/3/13	·095	744	—	—	,, ,, ($1·23 \times 10^{-7}$,,) ,, ,, ($2·61 \times 10^{-7}$,,)
31/3/13	·077	755	—	—	,, ,, ($1·38 \times 10^{-7}$,,)
1/4/13	·082 ·038	763 21½	·045	·037	From 2/4/13 to 1/5/13 electroscope unused.
1/5/13	·104 ·047	760 17½	·058	·046	
					Insulation broke down in August. Repaired in September. Five Ra estimations in October and November (cf. Fig. 1).
28/11/13	·048 ·032	764 36½	·017	·031	
29/11/13	·044	771	—	—	
1/12/13	·045	765	—	—	Emanation of $2·5 \times 10^{-7}$ mgr. Ra (equilibrium) introduced into electroscope for 3 hours (A).
2/12/13	·044	764	—	—	
3/12/13	·049	756	—	—	
4/12/13	·051	747	—	—	
5/12/13	·053	755	—	—	,, ,, ,, (B).
6/12/13	·087	752	—	—	
7/12/13	·084	763	—	—	
8/12/13	·079 ·025	755 23	·055	·024	
9/12/13	·046	764	—	—	,, ,, ,, (C).
10/12/13	·041	767	—	—	
11/12/13	·041	767	—	—	
12/12/13	·040 ·021	761 34½	·017	·023	
13/12/13	·043	768	—	—	,, ,, for 43 hours (D).
15/12/13 (a)	·203 ·094	768 38	·114	·089	
(b)	·134 ·070	768 41	·067	·067	Decay of active deposit after removal of emanation.
(c)	·069 ·043	768 33½	·027	·042	
(d)	·061 ·040	768 36	·022	·039	
16/12/13	·048 ·024	765 39	·025	·023	
17/12/13	·043 ·023	772 43	·021	·022	
18/12/13	·043 ·022	774 49	·022	·021	
19/12/13	·048 ·021	775 48	·029	·019	
20/12/13	·041 ·022	776 63	·021	·020	
22/12/13	·043 ·020	771½ 48	·025	·019	

CONDENSED PROTOCOLS OF EXPERIMENTS IN SERIES II B—*continued.*

Date.	Leak, div. min.	Air Pressure. mm. Hg.	Leak at Atmospheric Pressure due to— Air.	Instrument.	Remarks.
23/12/13	·044 ·019	759 50	·026	·018	
24/12/13	·045 ·021	756 43	·025	·020	Observations discontinued but electroscope kept charged.
5/1/14	·045 ·020	754 18½	·026	·020	
6/1/14	·042 ·020	751 23	·023	·019	
7/1/14	·056 ·021	766½ 22	·037	·020	
8/1/14	·048 ·021	763 22½	·028	·020	
9/1/14	·045 ·021	762 22	·025	·021	
12/1/14	·055	774½	—	—	Emanation of $2·5 \times 10^{-7}$ mgr. Ra (equilibrium) introduced into electroscope for 43 hours (A).
14/1/14 (a)	·058 ·024	768 40	·036	·022	Observations 7th to 14th hours after triple exhaustion of electroscope.
14/1/14 (b)	·058 ·025	768 39	·035	·023	
15/1/14	·075 ·026	767 41	·052	·023	Discarded. On 21st a fine hair was found attached to the standard for the gold leaf and was removed.
16/1/14	·068 ·027	764½ 36	·043	·025	
17/1/14	·063 ·026	756 42	·040	·024	
18/1/14	·066 ·030	764 43	·038	·028	
19/1/14	·072 ·031	761 41	·043	·029	
20/1/14	·067 ·032	761 42½	·037	·030	
21/1/14	·089 ·034	764 49½	·059	·030	N.L. Control electroscope = ·074 div./min.
22/1/14	·046 ·020	765½ 28	·027	·019	,, ,, = ·075 ,,
23/1/14	·051 ·020	765½ 26	·032	·019	,, ,, = ·077 ,,
24/1/14	—	—	—	—	Emanation of $2·5 \times 10^{-7}$ mgr. Ra (equilibrium) introduced into electroscope for 48 hours (B).
26/1/14 (a)	·263 ·033	763 16	·235	·028	After 1st exhaustion — Decay of active deposit.
26/1/14 (b)	·107 ·030	763 19	·079	·028	,, 2nd ,,
26/1/14 (c)	·056 ·021	764 18	·036	·020	,, 3rd ,,
27/1/14	·048 ·019	764 20½	·030	·018	N.L. Control electroscope = ·079 div./min.
28/1/14	·045 ·019	766 20	·027	·018	,, ,, = ·079 ,,
29/1/14	·042 ·020	762½ 16	·022	·019	,, ,, = ·080 ,,

Condensed Protocols of Experiments in Series II B—*continued*.

Date.	Leak, div. min.	Air Pressure, mm. Hg.	Leak at Atmospheric Pressure due to— Air.	Instrument.	Remarks.
30/1/14	·038 ·018	760½ 18	·020	·018	N.L. Control electroscope = ·077 div./min.
31/1/14	·040 ·018	761½ 17½	·023	·017	,, ,, = ·080 ,,
1/2/14	·038 ·018	765 18	·021	·017	,, ,, —
2/2/14	·041 ·018	765½ 18	·023	·018	,, ,, = ·080 ,,
3/2/14	·041 ·017	764 19½	·024	·017	,, ,, = ·078 ,,
4/2/14	·043 ·017	764 20	·027	·016	,, ,, = ·081
5/2/14	·043 ·018	764 20	·026	·017	,, ,, = ·085 ,,
6/2/14	·046 ·018	760 17	·029	·017	,, ,, = ·082 ,,
7/2/14	·042 ·017	756 18	·025	·017	,, ,, = ·082 ,,
8/2/14	—	—	—	—	,, ,, —
9/2/14	·040 ·018	757½ 18	·023	·017	,, ,, = ·084 ,,
10/2/14	·040 ·018	759 19	·023	·017	,, ,, = ·072 ,,
11/2/14	·041 ·017	755½ 17½	·025	·016	,, ,, = ·070 ,,
12/2/14	·041 ·017	753½ 19½	·024	·017	,, ,, = ·073 ,,
13/2/14	·042 ·017	760 19	·026	·016	,, ,, = ·070 ,,
14–15/2/14	—	—	—	—	,, ,, —
16/2/14	·040 ·018	762 19	·022	·018	,, ,, —
17/2/14	·043 ·021	764 19	·023	·020	,, ,, = ·091 ,,
18/2/14	·044 ·018	751 18	·026	·018	,, ,, = ·098 ,,
19/2/14	·043 ·017	750½ 17½	·027	·016	,, ,, = ·081 ,,
20/2/14	·043 ·017	754 18	·027	·016	,, ,, = ·086 ,,

THE CHANGES WHICH OCCUR IN MALIGNANT TUMOURS ON EXPOSURE TO THE GAMMA-RAYS OF RADIUM.*

By A. CLIFFORD MORSON.

During recent years great progress has been made both in this country and on the Continent in the treatment of malignant tumours by means of radium. To Wickham, Degrais, and Dominici, of Paris, we owe our present knowledge of radium therapy. So long ago as the year 1904, Wickham and Degrais first commenced to treat superficial growths with any degree of success, though four years previously Danlos, also of Paris, had tried the effect of radium upon cancer. However, the greatest advance in the use of this agent for therapeutic purposes was made by Dominici, who initiated the method of burying the tube containing the radium in the growth itself. Further, this same observer carried out an investigation into the microscopic changes which take place more especially in sarcomata when exposed to the rays of radium.

For some months I have been carrying out an investigation into the changes which take place in the cells of malignant growths when exposed to the gamma-rays of radium. The procedure which I have adopted in this investigation is as follows:—

A small portion of the growth is removed before exposure to these rays for the purpose of comparison between the radiated and the non-radiated cancer cell. On removal of the tube of radium, which in every case was embedded in the tumour for periods varying from fifteen to twenty-four hours, that part of the growth in actual contact with the tube of radium was excised. Further portions of the tumour were removed for microscopical examination at intervals of forty-eight hours to two months.

* Reprinted from the "Proceedings of the Royal Society of Medicine," 1914, vol. vii. (Pathological Section), pp. 97–108.

The tissues submitted to the action of the gamma-rays when removed by the scalpel appeared to be completely insensitive, and it was not found necessary to make use of either general or local anæsthesia in performing the operation. I have had personal experience of the anæsthesia produced by the gamma-rays, for last July, as a result of handling radium daily over a period of two months, changes

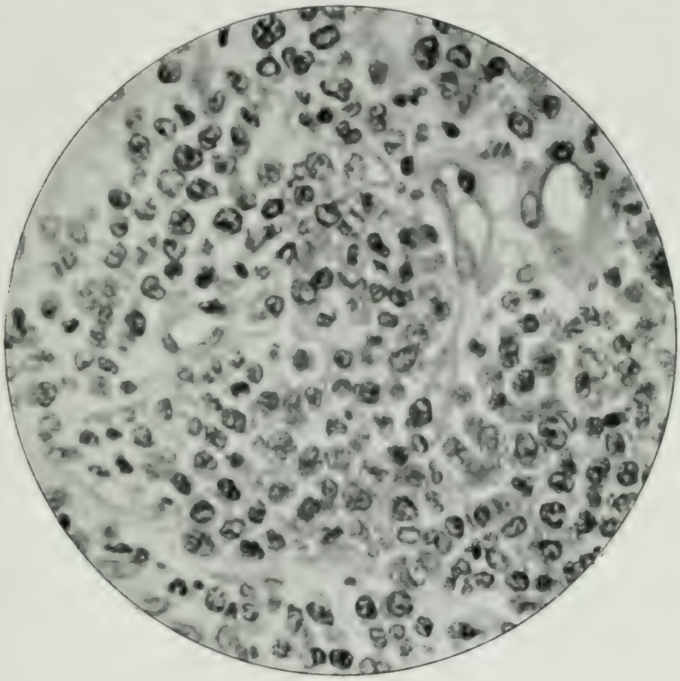


FIG. 1.

Round cell sarcoma: appearance before exposure to the gamma-rays.

occurred in the skin of the forefinger and thumb of my right hand, which caused a temporary loss of tactile sensation, but marked sensibility to heat and cold.

Within fifteen hours of the commencement of radiation the malignant cells in the immediate vicinity of the tube of radium begin to degenerate. The nuclei become irregular in shape and in places are broken up into two or more fragments. Twenty-four hours later all that can be seen is a structureless mass, embedded in which are a number of cells

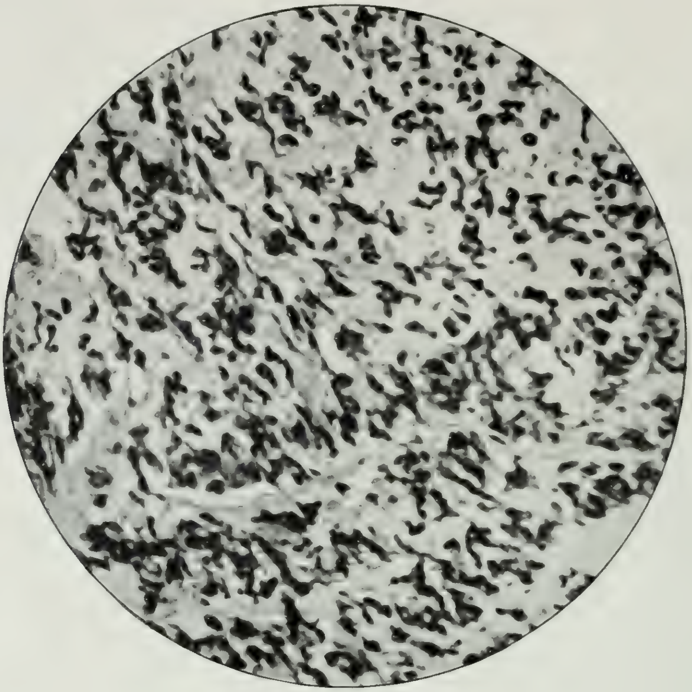


Fig. 2.

Appearance of growth (Fig. 1) twenty-four hours after commencement of treatment with 90 mgr. of radium bromide. (Same magnification as Fig. 1.)

in various stages of degeneration (Figs. 1, 2, 3, and 4). In the region of the growth where the intensity of the rays is less the cells may also be seen to be altered. Their normal arrangement is lost and the malignant mass is broken up into isolated groups of cells.

In some microscopic sections a definite line of demarcation has been seen between fully degenerated cells and the relatively unaltered malignant cells (Fig. 6). It is possible that this observation may assist in determining the radius of action of a known quantity of radium, when inserted into a growth whose microscopic characters have been previously investigated. If, three days following radiation, a part of what remains of the growth be removed, further changes will be noted. The connective tissue cells have commenced to proliferate, and those malignant cells which have escaped

immediate death show apparent vacuolation with greatly enlarged nuclei (Figs. 7 and 8).

In a considerable number of cases, within fourteen days of the application of the radium absence of cancer cells can be demonstrated.

On the other hand, some growths appear more resistant to the action of the gamma-rays and if microscopic examination be made as long as two months after radiation, malignant cells will be detected, though changed from the normal. The cells show a peculiar vacuolated appearance, with swollen nuclei. Around the malignant cells will be observed dense fibrous tissue.

It has been suggested that the rapid degeneration of the cells of a carcinoma when exposed to the gamma-rays is due to the presence of the metal tube containing the radium. To clear up this point I performed a test experiment. A silver

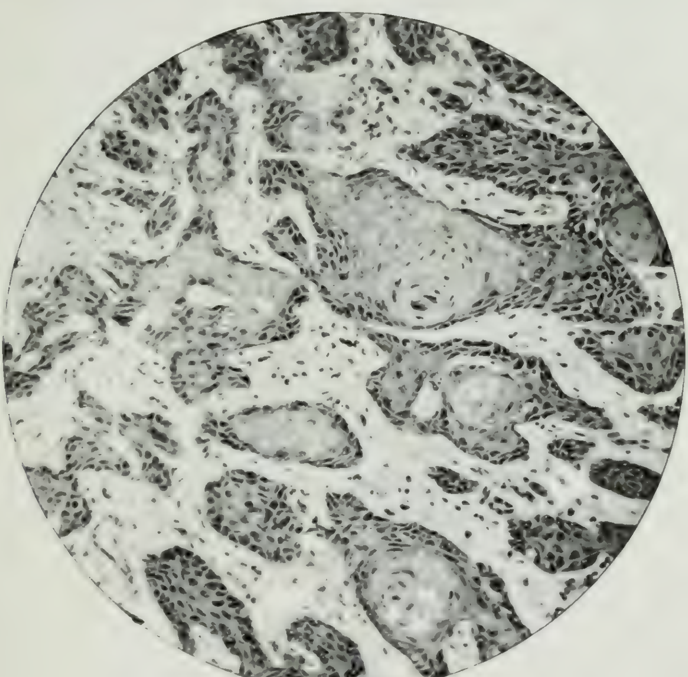


FIG. 3.

Squamous cell carcinoma of upper lip; appearance before exposure to the gamma-rays.

tube $1\frac{1}{8}$ in. long, one end of which contained 40 mgr. of radium bromide, was inserted into a recurrent mammary growth in the skin for twenty hours. At the end of this time that

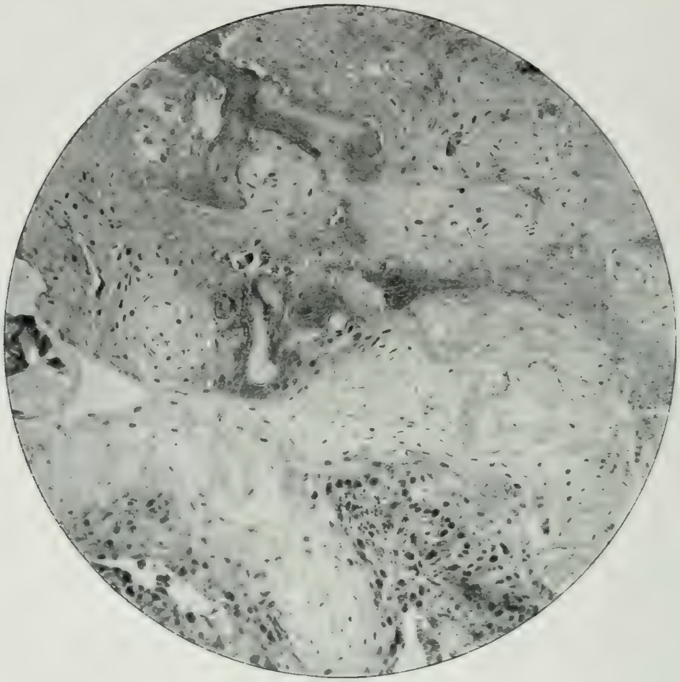


FIG. 4.

Appearance of growth (Fig. 3) forty-eight hours after commencement of treatment with 90 mgr. of radium bromide. (Same magnification as Fig. 3.)

portion of growth in contact with the whole length of the tube was removed. Microscopic examination showed that only those cells which were in the neighbourhood of the radium were degenerating. The growth in contact with that part of the silver tube containing no radium was unaltered (Fig. 9). It will be seen, therefore, that the effect of exposing malignant growths to the gamma-rays of radium is two-fold: (*a*) Rapid degeneration of the malignant cells in the immediate vicinity of the tube of radium; (*b*) apparent vacuolation and enlargement of nuclei of those cells beyond the degeneration zone.

The action of the radium on the connective tissue cells shows its similarity to the attempt of Nature to arrest the

growth of cancer through overgrowth of fibrous tissue. Considerable difficulty arises when an attempt is made to interpret the meaning of the changes which I have described. Wedd and Russ have exposed mouse carcinoma outside the body to the beta- and gamma-rays from an intensity of 2 mgr. of radium bromide per square centimetre for periods varying from one to twenty-four hours and failed to find any microscopic changes unless the irradiated tumour were re-inoculated; yet when the cells of human carcinoma are exposed in the body to the gamma-rays profound alterations are detected. These observations suggest that the tissue fluids must play some part in causing so rapid a degeneration of the malignant cell. It is quite possible that the change produced in the cancer cell by the rays of radium is a

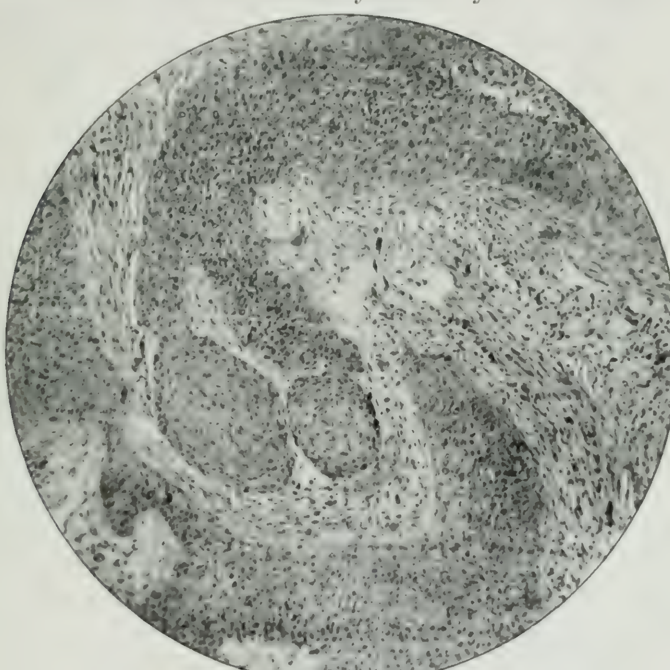


FIG. 5.

Squamous cell carcinoma of ear; appearance before exposure to the gamma-rays.

chemical one, and it is only when in contact with certain constituents of the blood or lymph that these degenerative changes can take effect.

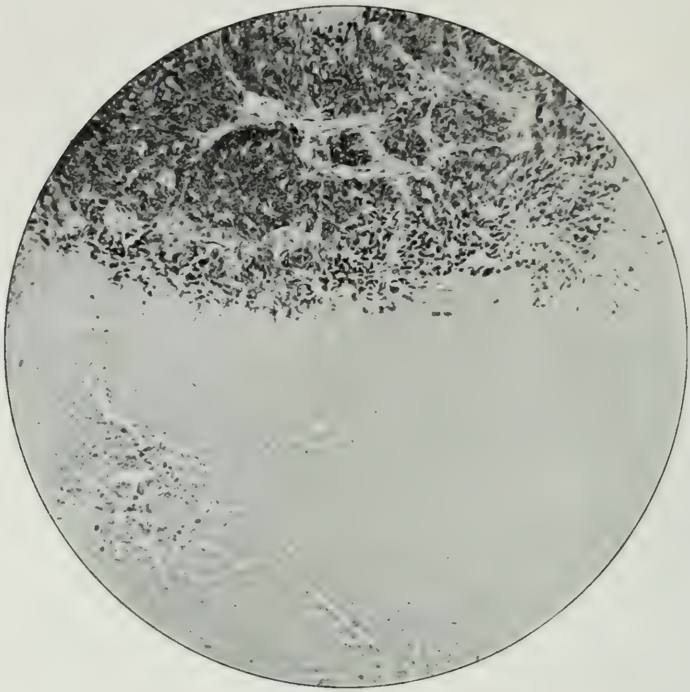


Fig. 6.

Appearance of growth (Fig. 5) twenty-four hours after commencement of treatment with 150 mgr. of radium bromide, showing the line of demarcation between the degenerated cells and the relatively unaltered malignant cell.

A knowledge of the degree of sensibility of different types of malignant cells, on exposure to the gamma-rays, is, in my opinion, the keystone to improvement of treatment of cancer with radium. I have found that the cells of those tumours, which by ordinary methods of histological diagnosis appear to be round cell sarcoma, are very sensitive to the action of radium. On the contrary, the spindle cells of a periosteal sarcoma are more resistant to the rays.

Turning to the carcinomata, we find remarkable differences in sensibility. In the squamous cell variety degenerative changes in the cells, such as keratinisation, tend to be increased by exposure to radiation. Further investigation is needed to explain why the sensitiveness of squamous cell carcinoma of the cervix uteri, as I have found it to be, is greater in those cases which give rise to severe hæmorrhage

than in other varieties. With regard to columnar cell carcinoma, both Dominici and Degrais have pointed out the great resistance of this type of growth to the rays. It is difficult to understand why this should be so, for columnar cells are well recognised as the most delicate of epithelial structures. My experience of the effect of the gamma-rays on different varieties of spheroidal cell carcinoma is too limited for a definite statement to be made. The difficulty of carrying out a systematic microscopical investigation of cases of carcinoma of the breast is obvious.

I have already pointed out that three days after radiation the connective tissue cells show proliferation. This overgrowth of the connective tissue elements of a carcinomatous tumour has an important bearing on the subsequent changes

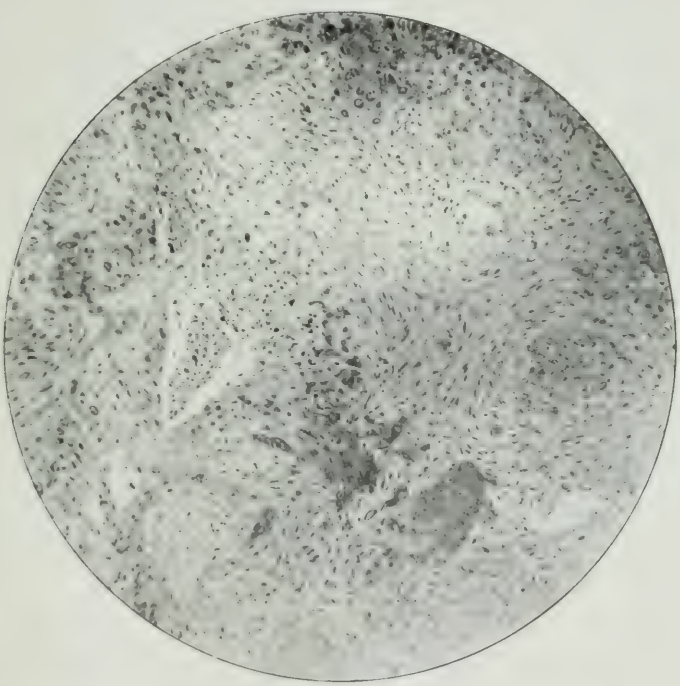


Fig. 7.

Appearance of growth (Fig. 5) three days after treatment with 150 mgr. of radium bromide, and at a distance of about 1 in. from where tube of radium was inserted. This section shows the proliferation of the connective tissue cells. (Figs. 5, 6, and 7, same magnification.)

in those cancer cells which may have escaped immediate destruction on exposure to the gamma-rays. It is not improbable that in course of time malignant cells which had survived radiation would be killed by the contraction of newly formed connective tissue.

Investigators of the effect of radium upon pathological tissues have now fully recognised that the action of this therapeutic agent is essentially a selective one.

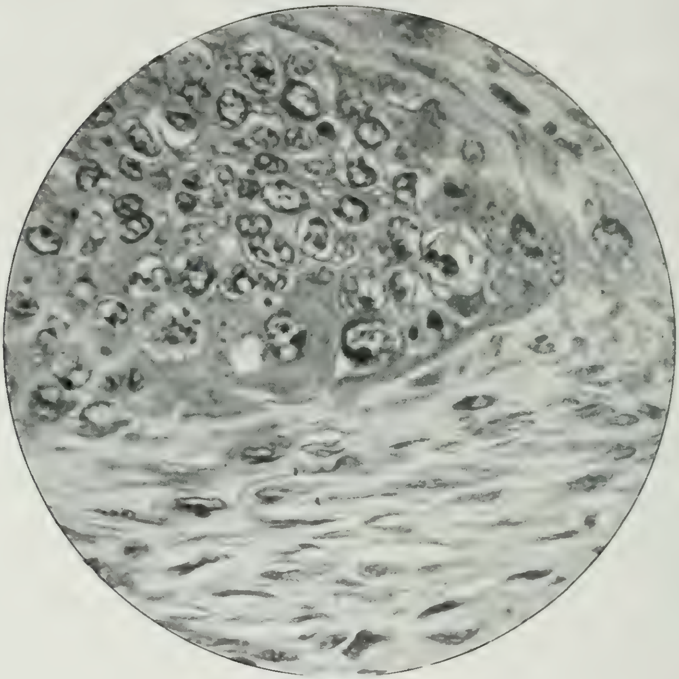


FIG. 8.

Appearance of growth (Fig. 7) under high magnification, showing apparent vacuolation and enlargement of nuclei of the malignant cells.

It has not yet been determined whether the proliferation of connective tissue cells, which follows destruction of malignant cells, is due to the rays themselves or is the result of their action on the cancer cell.

A study of the changes, if any, which may take place in metastases following radiation of the primary growth has, as far as I am aware, never been attempted in this country. A statement on this subject must necessarily be guarded at the

present time, for the evidence in favour of any change is extremely slender. However, in the case of secondary deposits in lymphatic glands, though the material at my

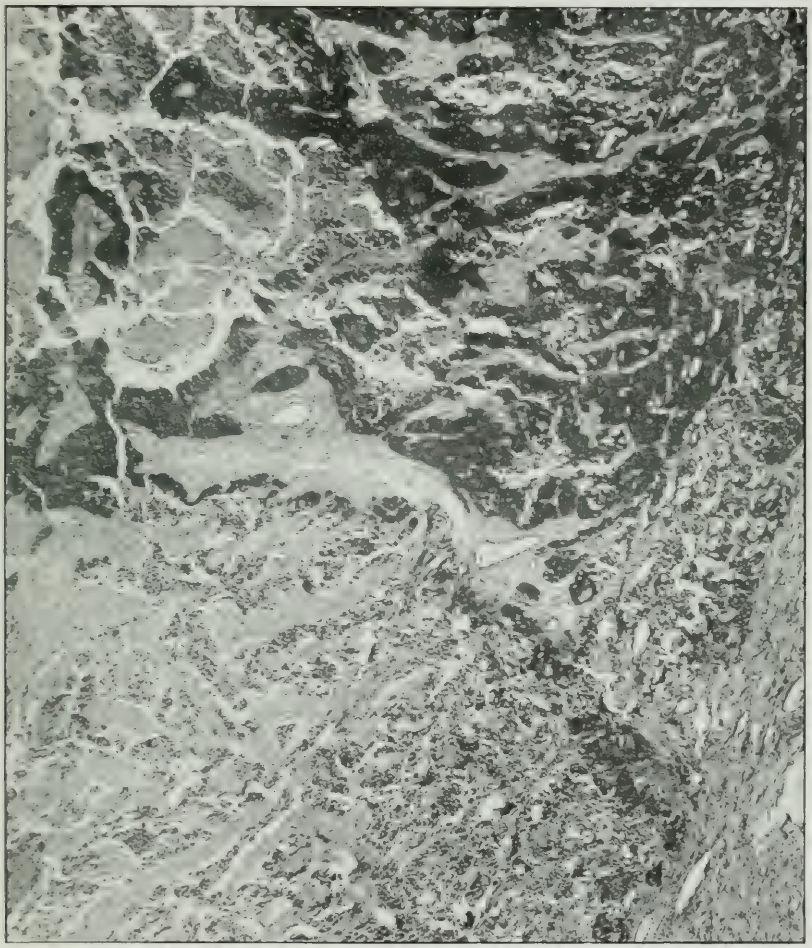


FIG. 9.

Photomicrograph of carcinoma of breast showing the unaltered growth in contact with the part of the silver tube containing no radium, and the degenerated growth in contact with that which contained 40 mgr. of radium bromide. (Low magnification.)

disposal has been limited to four cases, I have observed slight changes which encourage me to make further investigations.

At a meeting of the Clinical Section of the Society in December, 1913, Mr. T. H. Kellock showed a patient* in whom a tumour of the tongue disappeared under radium treatment. Following the exposure of the growth to the rays, the glands in the neck became smaller and more movable. Two months later, as the glands were still palpable, it was decided to remove them by operation. I was present at the operation, and I can state with confidence that I have never seen enlarged glands, secondary to a growth of the tongue, dissected out with such little difficulty. Considerable difference of opinion was manifested at the meeting as to the nature of the growth in these glands. I think it is possible that the difficulty in diagnosis was due to the change which had taken place in the malignant cells following the disappearance of the primary tumour. Since this case was published I have had the opportunity of noting in two other patients a similar decrease in the size of lymphatic glands following exposure of the primary growth to the gamma-rays.

Recently, through the kindness of Mr. Bonney, I was able to secure a microscopic section of a metastasis in a lymphatic gland secondary to squamous cell carcinoma of the cervix uteri treated with radium (Figs. 10 and 11). It is well recognised that the cellularity of metastases is at least as great as that of the primary growth. This is especially so in the case of lymphatic glands. Yet the microscopic picture of the metastasis in this case shows but a few islands of malignant cells, surrounded by a mass of newly formed connective tissue. I have examined a number of sections of gland metastases of squamous cell carcinoma of the cervix uteri and failed to find in them the least resemblance to this specimen in respect of the amount of fibrous tissue. Are such changes, macroscopic and microscopic, as I have described in lymphatic gland metastases due to the direct action of the gamma-rays of radium? If a gland metastasis is so near to the radiated primary growth as to be exposed to rays of great intensity in sufficient quantity, changes in the malignant cells will certainly occur. However, in the cases I have seen, some of the metastases have been at such a

* "Proceedings Roy. Soc. Med.," 1914, vii (Clin. Sect.), p. 45.

distance from the primary growth as to preclude any possibility of their being directly affected by the rays. It is possible that the absorption of degenerated and degenerating cancer cells at the primary site due to exposure to the gamma-rays leads to the formation of some substance which not only retards the growth of the malignant cell at a distance, but also stimulates the connective tissue cells to proliferate.

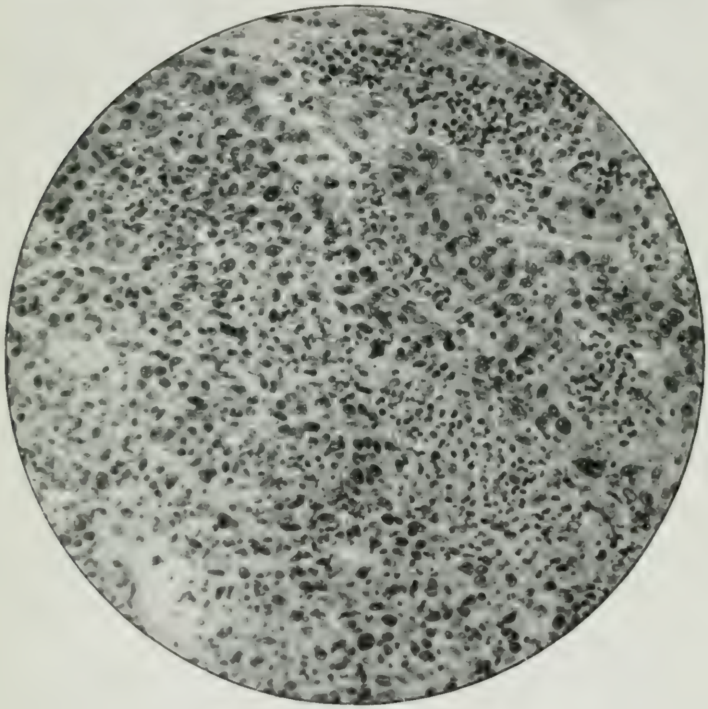


FIG. 10.

Squamous cell carcinoma of cervix uteri.

Evidence was brought before the Pathological Society of Great Britain and Ireland at the January meeting, in a paper by B. H. Wedd, A. C. Morson, and S. Russ,* that the cells of mouse carcinoma when irradiated by radium can confer immunity, so that a graft of non-radiated tumour when inoculated does not grow. Whether the cells of human

* See also this vol., p 71.

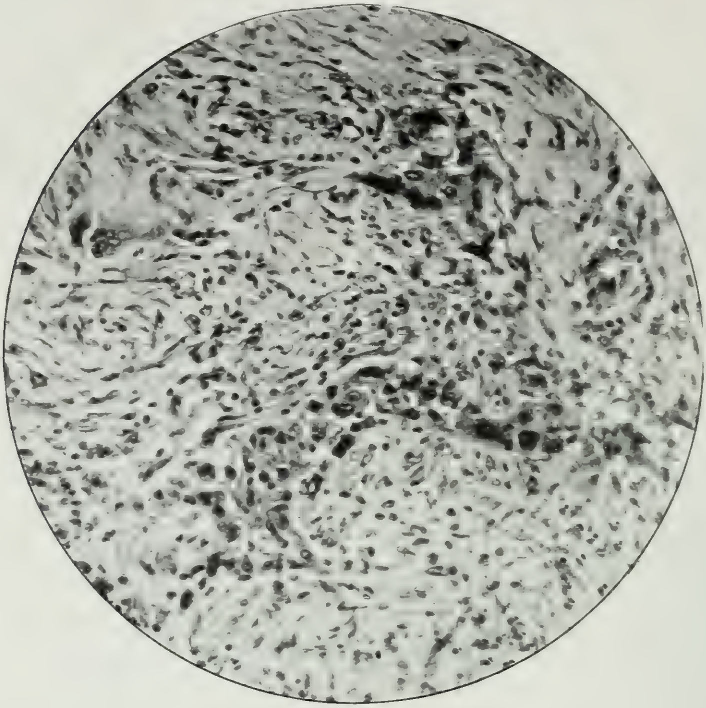


Fig. 11.

Appearance of lymphatic gland metastasis one month after primary growth (Fig. 10) had been exposed to radiation. (Same magnification as Fig. 10.)

carcinoma which disappear in the body when exposed to radium likewise confer any degree of immunity can only be settled by further investigations.

Much research work remains to be done before we can place radium therapy, in relation to the treatment of cancer, on a sound scientific basis. At the present time, all that we can claim is that certain microscopic and macroscopic observations have been made which compel us to continue this line of research.

SOME EXPERIMENTS ON THE ACTION OF THE BETA AND GAMMA RAYS UPON ANIMAL TISSUES.

By H. BECKTON.

THE changes which take place in the tissues of malignant new growths when exposed in the living body to the action of quantities of radium bromide of the order of 100 milligrams have been described by Morson.[1] The question arises, "Are these changes due to the direct action of the radium upon the tissue cells, or are they secondary changes and due to the action of the body fluids and the cells carried by these upon the irradiated tissues?"

In the present investigation an attempt has been made to determine whether radium radiations directly produce histologically recognisable changes which may be regarded as initial steps in the degradation of the cell.

I. As regards excised tissues, Russ and I[2] found that alpha radiations give rise to striking changes both in nuclei and Altmann's granules, the nuclei showing diffusion of chromatin and the granules a very marked tendency to, or even complete, disappearance. In the case of beta and gamma radiations, however, my own work confirms and extends the observations of those who have failed to find any histological changes in excised tissues exposed to these rays. Since the results of nearly a hundred experiments have been negative, it is unnecessary to describe them in full detail. Briefly, the quantities of radium employed, estimated as bromide, varied from 25 to 100 milligrams. It was used either as a solid contained in platinum or silver tubes, or as emanation enclosed in thin glass tubes surrounded or not by silver tubes. The tissues investigated were spleen, liver, and kidney of rat; small portions of these were irradiated at distances varying from contact (the tissues in some cases

actually touching the tubes, in others being separated from them only by thin films of mica) to 30 cm. Appropriate controls were used in each experiment. The duration of exposure to the action of radium varied (*a*) from 1 to 3 hours, and (*b*) from 1 to 3 days. The radiated and control tissues were alike fixed and stained in the manner described elsewhere[3] for Altmann's granules as well as for nuclear detail, and in neither respect did the radiated tissues show any marked or constant differences from the corresponding controls. These experiments were extended by allowing portions of both irradiated and control tissues, after removal of the former from the influence of radium, to undergo autolysis at room-temperature (at which all the experiments were carried out) for further periods of from 1 to 3 days. Even under these conditions no definite differences were observed, so that the invisible changes produced by radium during exposure do not become manifest in excised tissues at a later date.

This absence of difference between irradiated and control tissues also indicates that autolytic ferments present in the various tissues investigated are unaltered by the direct action of radium.

II. Small living tadpoles were exposed, in drops of water placed between thin films of mica, to beta and gamma radiations from 24 mgr. of radium bromide disposed over a circle ·8 cm. in diameter. The drop of water had in each case a diameter just less than this. The radium capsule, tadpole, &c., were kept in a saturated atmosphere, so that the drop of water in which the tadpole was placed retained its original size. A control experiment was performed in each case. In every instance the experimental tadpole was killed sooner or later by the radiations, while the corresponding control was still alive and well, as shown by its vigorous movements. Two experiments showed that under the conditions specified the animals were able to support irradiation for a little over seven hours.

Upon removal from the water the tadpoles, experimental (dead) and control (living), were placed in formol-Müller, (formalin 2 vols., Müller's fluid 98 vols.) and ultimately stained for Altmann's granules and also with hæmatoxylin

and eosin. In the case of two tadpoles which were placed in the fixing fluid immediately after death no differences were found in respect of either Altmann's granules or nuclei between these and the corresponding controls; in the other cases the granules had disappeared from the irradiated tadpoles, presumably owing to post-mortem changes.

It is thus apparent that radium (beta and gamma radiations together) acting upon the whole organism can produce changes resulting in death without affecting the Altmann's granules of the cells as shown by the above method.

In this connection it is of interest to mention the results of some observations regarding the action of radium upon certain Infusoria. Drops of water containing Vorticellæ and several other types of unicellular organisms were exposed to the action of capsules containing respectively 3 and 7 mgr. of radium bromide. Here again it was found that the organisms stained immediately after being killed by radium showed Altmann's granules in the same way as the corresponding controls.

Conclusions.

From the foregoing it appears that, while alpha radiations on the one hand may directly give rise to histologically recognisable changes by their action on animal cells, beta and gamma radiations on the other hand fail to do so. Hence the marked tissue changes observed by Morson in the treatment of malignant disease by beta and gamma radiations must be dependent upon the intervention of the fluids of the living body. In other words, the irradiated cells, although showing no recognisable histological changes, are altered in such a way that they now act as irritant foreign bodies.

References.

[1] Morson, "Proceedings of the Royal Society of Medicine," 1914, vol. vii, (Pathological Section), p. 97. (Cf. also this vol., p. 110.

[2] Beckton and Russ, "Archives of the Middlesex Hospital," 10th Cancer Report, 1911, p. 99.

[3] Beckton, "Archives of the Middlesex Hospital," 9th Cancer Report, 1910, p. 115; "British Medical Journal," 1909, vol. ii, p. 859.

A SERIES OF CASES OF CARCINOMA EXAMINED BY THE WASSERMANN METHOD.

By H. MAC CORMAC and A. CLIFFORD MORSON.

Object.—The examination was undertaken to determine whether syphilis predisposes to carcinoma and, if so, whether in general or only in certain regions.

Methods.—The Wassermann reaction in the original technique was invariably employed. The method described below was followed in a great majority of cases.

One modification was of necessity made—the test was carried out in one-tenth volumes, as we found it impossible to obtain 5 cc. or 10 cc. of blood from patients who suffer from cancer; this tended to cause some disturbance, and the patients themselves object to the abstraction of more than a small quantity of blood.

This modification while undesirable was, under these particular circumstances, unavoidable.

In view of the somewhat unexpected findings in tongue cases it is appropriate to ask how accurate the test is. Here it may be stated that the sera from cancer cases were always tested along with the blood in a series of known syphilitic and non-syphilitic patients, and that the test in those patients whose clinical condition was known proved to be perfectly accurate. The importance of employing a sensitive antigen cannot be over emphasised, and we have found that described by M. A. Desmoulière (Comptes rendus des séances de l'Académie des sciences, t. 155, p. 927) to fulfil this requirement to a high degree. We give below his method of preparation of the antigen, and the technique for the Wassermann test as described in the paper quoted above.

Preparation of Antigen.

The liver, preferably of a syphilitic fœtus, or from a pig if this cannot be obtained, is dried in vacuo and powdered.

This is extracted with ether in a long glass funnel until nothing more comes out from the powder. It is then dried, first in the air and subsequently at 37°C.

One gram of this powder is treated for 72 hours at 37° C. with 20 cc. of alsolute alcohol in a well-closed flask, shaking from time to time. This is then filtered, and 10 cc. of the filtrate is added to 0·1 gram of *pure* Cholesterin.

For use this concentrated antigen is diluted 1 in 15 with physiological saline. In the reaction 0·3 cc. is employed.

Before the actual test is carried out it is necessary to determine the power of the complement to be used. This is an essential and should never be neglected. It is carried out as follows :—To each of three glass tubes are added 2 cc. of physiological saline and 0·3 cc. of the diluted antigen. Then 0·1 cc., 0·15 cc. and 0·2 cc. of 50 per cent. guinea-pig serum is put into the respective tubes; these are incubated for one hour at 37° C. Finally 0·1 cc. of titrated amboceptor (anti-sheep), and 0·1 cc. of a 50 per cent. dilution of sheep cells (washed and defibrinated in the usual way) are put into each tube and the mixture incubated for half an hour. The dose of complement selected is the smallest which causes complete hæmolysis in this time. In the subsequent Wassermann test two tubes are employed for each serum. Into one 2 cc. of physiological saline, 0·2 cc. of decomplemented serum, 0·3 cc. of antigen and the already determined dose of complement are added. The second tube contains similar reagents but no antigen. After one hour in the incubator, 0·1 cc. of titrated amboceptor and 0·1 cc. of sheep-cell emulsion are mixed into each tube, and a reading made after a further period of half an hour at 37° C. A positive result has only been accepted in cases where complete inhibition of hæmolyses occurred.

The only obvious criticism that can be directed against this method is that it is too sensitive. In other words, our series of cases give, if anything, too great a number of positive results.

In the results set forth below each table shows (1) the total number of cases tested, (2) the relative proportion of males to females, (3) how many cases gave positive results from a blood test, (4) in how many a history of syphilis was obtained clinically, and finally (5) the total number of

syphilitic cases as obtained by both methods. It must be accepted that a not inconsiderable number were latent—that is to say, although a history of syphilis might be obtained, the blood result was negative. Again in a certain proportion, although the blood was positive, no previous history of infection could be obtained from the patient.

Table I.—Carcinoma of Cervix.

No. of Cases.	M.	F.	+ Clin.	+ W.	Total No. of + ve Cases.
13	—	13	0	2	2

In the above series 15·4 per cent. showed evidence of syphilis. This is a high proportion, and possibly with a larger number of cases a different result might be obtained.

Table II.—Carcinoma of Breast.

No. of Cases.	M.	F.	+ Clin.	+ W	Total No. of + ve Cases.
21	—	21	0	0	0

This latter compares unexpectedly with the above. It suggests that the spirochæte has little predisposing influence for carcinoma in this region.

Mouth Region.

It has long been held by clinicians that cancer of the mouth, tongue, etc., is frequently associated with, and results from, previous syphilitic disease of this region. Our results are given below.

Out of a total of 46 cases of carcinoma in this region, positive evidence of syphilis is obtained in 10 cases, a percentage of 21·7. In the case of the tongue alone the percentage is higher still, being 26·1, more than a quarter of the cases. This finding is smaller than that given by some other observers. But, as we have already pointed out, our method

TABLE III.

Region.	Total No.	M.	F.	+ Clin.	+ W.	Total No. of + ve Cases.
Tongue	23	20	3	4	4	6
Lip	5	5	—	1	1	1
Cheek	2	2		0	0	0
Floor of Mouth ...	7	7	—	2	1	2
Tonsil	1	1		0	0	0
Fauces	3	1	2	0	1	1
Palate	5	4	1	0	0	0

is a particularly sensitive one, and error, if such should occur, would rather be in the direction of increasing the percentage. It is nevertheless probable that the figure is too low, for clinical evidence of previous syphilitic infection in malignant disease of the tongue is frequent; apart from latent cases, accounting for a certain number, it would appear that the negative Wassermann results in tongue and mouth carcinoma are met with more frequently than might be expected. We have no explanation of this fact, and state it as an impression that has been suggested to us in our work.

TABLE IV.—ALIMENTARY CANAL.

Region.	Total No.	M.	F.	+ Clin.	+ W.	Total No. of + ve Cases.
Œsophagus ...	4	4		1	0	1
Pancreas	1	-	1	0	0	0
Stomach	9	7	2	0	2	2
Rectum	17	13	4	1	1	1
Large Intestine ...	2	1	1	0	0	0
Gall Bladder ...	1	-	1	0	0	0
"Abdomen" ...	1	-	1	0	0	0

In a total number of 35 cases, there are found 4 in whom evidence of syphilis was obtainable, a percentage of 11·4.

TABLE V.—MISCELLANEOUS.

Region.	Total No.	M.	F.	+ Clin.	+ W.	Total No. of + ve Cases.
Ethmoid	1	1	0	1	0	1
Kidney	1	-	1	0	0	0
Prostate	3	3	- -	1	0	1
Lungs	1	1	0	0	0	0
Sup. Maxilla ...	1	1	0	0	0	0
Larynx	11	9	2	1	1	2
Rodent Ulcer ...	3	3	0	0	0	0
Sarcoma	1	—	1	1	1	1

Out of 22 miscellaneous cases, positive results were obtained in 5, that is, 22·7 per cent. In the above table the large proportion of syphilis with squamous carcinoma is again noticeable (the larynx).

CONCLUSIONS.

We have examined a total number of 137 cases of carcinoma of various regions, and we find evidence of previous syphilitic infection in twenty-one instances, a percentage of 15·3. This is certainly high, considerably higher than would be obtained from an equal number of individuals taken at random. No reliable information as to the incidence of syphilis among a population is to be had; statistics recently brought forward, based on results obtained from blood taken post mortem or during chloroform anæsthesia, are quite worthless, and do not demand serious attention.

Particularly noticeable is the frequent association of the two diseases in squamous carcinoma in all regions, probably 20·8 per cent. It is, therefore, probable that with more thorough treatment of the earlier stages of venereal disease carcinoma will be to some considerable extent diminished.

EXPERIMENTS UPON THE INFLUENCE OF PLATINUM SCREENS WITH A VIEW TO DETERMINING THEIR VALUE IN THE RADIUM TREATMENT OF MALIGNANT DISEASE.

BY W. S. LAZARUS-BARLOW.

IN another paper (p. 34) I have brought forward reasons for believing that the distributions of quantity and time in calculating a "radium dose" must be different in order to bring about an optimum result when treating (*a*) a columnar cell carcinoma, (*b*) a *moist* squamous cell carcinoma, (*c*) a *dry* squamous cell carcinoma. Not less important in respect of treatment is the question of "screening." This question has been examined experimentally, and the results are given below.

The object of introducing screens is to eliminate all but the hardest types of gamma rays, and the denser and thicker the screens the better this object is attained. In practice, silver, lead, and platinum screens are used, but in the present research, platinum screens were employed, if we omit mention of the solid paraffin screens which were introduced for another purpose.

The experiments were carried out with a tube of platinum (·5 mm.) containing 92 mgr. $RaBr_2 2H_20$. This tube was 18 mm. long and 3·5 mm. in diameter. It was fitted with three detachable platinum screens, respectively ·5, 1·0 and 1·5 mm. in thickness, so that it was possible to determine the effects of radium screened through ·5, 1·0, 1·5, and 2·0 mm. of platinum. The screens were in the form of platinum tubes with screw caps into which the radium tube could be inserted.

Use was again made of the lower end of the rectum and the adjacent cutaneous surface of the tail in the rat, half of the length of the radium tube (without or with screen) lying

proximal to the sphincter ani, i.e., within the gut, and half lying distally, i.e., in contact with the skin of the root of the tail.

Owing to the superposition of screens of varying thickness it was clear that unless special precautions were taken (*a*) the radium would be acting at different distances from the tissues, and (*b*) that the tissues would be distended to different degrees in the various portions of the experiment. Hence it was determined to coat the radium tube (with or without its screen) with that amount of paraffin wax which should bring the whole to a constant diameter of 8 mm. The only exceptions to this rule were in two experiments where a contrast was desired between the unscreened and the heavily-screened tube, as used in clinical work. The following series of conditions was therefore examined:—

A	92 mgr. $RaBr_2$ acting through	·5 mm Pt.	without Paraffin.
B	,,	·5 ,,	+ 2·0 mm. ,,
C	,,	1·0 ,,	+ 1·5 ,, ,,
D	,,	1·5 ,,	+ 1·0 ,, ,,
E	,,	2·0 ,,	+ 0·5 ,, ,,
F	,,	2·0 ,,	without ,,

In order that the ionisation value ("radium dose") should be constant throughout the experiments, electroscopic measurements were made, and it was found that an exposure to B for 15 minutes was equal to exposures of C for 16 minutes, D for 17 min. 10 sec., E and F for 18 min. 12 sec. The exposure to A was for 13½ minutes, and the values utilised were those obtained in the previous research (cf. Table I., p. 48).

Three rats were therefore exposed to irradiation under each of the conditions given above, and one animal of each series was killed on the third, sixth, and ninth days after irradiation. The histological procedure was identical with that described elsewhere (cf. p. 36), except that Pappenheim's stain was used throughout. For the "counts" of mitoses ten sections, 5μ thick, were used of each specimen, and every third section of the ribbon was taken so as to avoid counting the same mitosis twice. For the numbers of plasma cells three sections were taken.

In each region a length of 5 mm. was examined except the moist squamous region, where a length of 2·5 mm. was taken.

The condition of the tissues was considered in three regions, viz., dry cutaneous, moist squamous, columnar, all of which were in contact with the radium tube; and one region, viz., columnar, which lay at a short distance from the radium tube. Observations were made upon the reproductive activity of the epithelial cells, as indicated by the number of mitoses, and upon the degenerative and inflammatory condition of the epithelial cells and subjacent tissues, as indicated by the nuclei and cytoplasm of epithelial cells, muscle, presence of mucus and desquamation, numbers of plasma cells, etc. Thus data were obtained which may be divided into three groups—A, general conditions; B, plasma cells; C, mitoses.

A.—General Conditions.

It is not proposed to give detailed descriptions of the histological specimens. The following will, however, indicate the method after which the examination was carried out.

Rat exposed to radium acting through ·5 mm. platinum + 2 mm. paraffin.

High Columnar Epithelium Region.—Slight amount of mucus on surface, no desquamation of cells, much mucus in the glandular tubes, much mucoid degeneration of cytoplasm, nuclei of columnar cells swollen clear and pale, outlines of the cells lost. Muscularis mucosæ good, circular muscle greatly œdematous, broken, and muscle bundles small, longitudinal muscle good.

Low Columnar Epithelium Region.—Mucus present on surface, no desquamation, the glandular tubes are simply bags of mucus, cells are very degenerated, nuclei are obscure and degenerated. The muscularis mucosæ is thin and the nuclei stain poorly, circular muscle granular and œdematous, the nuclei being blue-edged, irregular, small, colourless rings, longitudinal muscle fibres are thin and the nuclei are pale, but the condition is better than in the other muscular regions.

Moist Squamous Epithelium Region.—Outlines of cells nearly lost, the nuclei being contracted and deeply staining

or mere colourless bags; superficially there is loosening and desquamation in plaques. Circular muscle as in low columnar region but less œdematous.

Dry Squamous Epithelium Region.—Superficial layers desquamated, nuclei of epithelial cells contracted or colourless, outlines of cells lost. Cells of hair follicles in a similar condition to the epidermis. Condition of sphincter ani muscle and of the local sebaceous gland good. Voluntary muscle granular and striation is lost, but the staining and shape of the nuclei are good; more distally striation becomes visible, but the bands are broadened.

When all the specimens had been described after the above fashion it was felt that the best way to present a picture of the results obtained was to "mark" them in the same way as is done with examination papers. Thus in the high and low columnar regions nuclei, cytoplasm, superficial mucus, mucus in tubes, desquamation, muscularis mucosæ, circular muscle, and longitudinal muscle were treated as "questions," and 10 marks were given as a maximum for excellence in respect of each. The moist and dry squamous regions were dealt with on similar lines. As a result certain totals were obtained which give in a simple, though admittedly rough, way some indication as to the degree of departure from the normal of the specimen under consideration. These totals are given in Table I. below.

That the values given in Table I. are roughly indicative of the condition of the tissues under consideration is rendered probable *a priori* by the great frequency with which the values for the animal of the ninth day after irradiation are higher than those for the animal of the third day. This statement is true in 20 out of the 24 sets of three values given. With the mild irradiation given it might be anticipated that by the ninth day after exposure to the rays any effect that might have been produced would be passing off.

Confining attention to the mean values it can be seen that the general condition of the epithelium and sub-epithelial tissues departs from the normal to a greater extent with slight platinum screening of the radium than with heavy screening. Naturally a perfect gradation according to thickness of screen cannot be expected under the conditions of the

Table I.

Table showing the degree of departure from normality of the epithelium and sub-epithelial tissues in irradiated rats, excluding mitoses and plasma cells. Normality = 100.

Screen for Ra.	Day after Irradiation.	High Columnar Region.	Region of Radium Tube. Low Columnar Region.	Moist Squamous Region.	Dry Squamous Region.
A					
·5 mm. Pt.	3	55	54	58	57
	7	66 } 67	64 } 66	68 } 65	52 } 59
	9	81	79	68	68
B					
·5 mm. Pt. + 2 mm. Paraffin.	3	64	44	54	47
	6	79 } 70	71 } 55	86 } 69	75 } 56
	9	65	50	66	47
C					
1 mm. Pt. + 1·5 mm. Paraffin.	3	54	55	64	37
	6	91 } 78	85 } 74	92 } 83	63 } 52
	9	89	81	92	57
D					
1·5 mm. Pt. + 1·0 mm. Paraffin.	3	76	54	62	42
	6	76 } 74	99 } 78	92 } 79	78 } 72
	9	71	80	84	95
E					
2·0 mm. Pt. + ·5 mm Paraffin.	3	69	68	96	68
	6	71 } 75	90 } 86	78 } 85	55 } 69
	9	84	100	80	85
F					
2·0 mm. Pt.	3	85	70	70	88
	6	79 } 86	79 } 80	58 } 73	78 } 79
	9	94	91	90	70

experiment, but contrast of the means for the A and F series and contrast of the means for the B and E series (in both of which pairs the conditions differed as little as possible except for the thickness of platinum screen involved) shows without exception that the general condition of the epithelium and sub-epithelial tissues is worse with the thinner screen. This is true whether one consider the columnar epithelium region at a distance from the radium tube or the columnar, moist squamous or dry squamous region in direct contact with the radium tube.

B.—Plasma Cells.

In respect of plasma cells the high and low columnar regions alone can be considered, since in the regions invested with squamous epithelium these cells are found neither under normal conditions nor in the altered conditions induced by such a degree of irradiation as was carried out in these experiments. The mean numbers per millimetre found in the various animals used for the experiments are indicated in Table II., whence it appears that there is a general tendency for the number of plasma cells to be greater on the ninth day after irradiation than on either the third or the sixth day. Again comparing the mean values for series A and F and those for series B and E, it is seen that the number of plasma cells is greater in the instance where the thinner platinum screen has been employed whether one consider the tissues in direct contact with the radium tube or those at a little distance. This difference manifested by the mean values is well borne out by examination of the individual pairs of observations to be contrasted; in 9 out of 12 pairs the number of plasma cells per millimetre of section is greater in that specimen where the radium was least heavily screened with platinum.

C.—Mitotic Figures.

The number of mitotic figures found per millimetre of section are set forth in Table II. From this table it appears that the mean numbers of mitotic figures, where the radium has been screened to the least degree (Series A), is higher than in any other series. This is absolutely true only if one consider the high columnar, low columnar, and the moist squamous cells, since the dry squamous cells do not comform. So, too, when considering Series A and F and Series B and E as heretofore, although it is generally true in the case of individual pairs of observations that with a thinner platinum screen the number of mitoses present is greater (16 out of the 24 pairs), this is not well borne out by the means. Examination of the means shows that the values in Series A are uniformly greater than the means for Series F, whereas three out of the four pairs of means in Series B and E go in the opposite direction.

TABLE II. *Table showing the numbers of mitotic figures and of plasma cells per millimetre in sections 5μ thick of rat's rectum and skin of tail after irradiation through different thicknesses of screen.*

	Normal.		Day after Irradiation.	A ·5 mm. Pt.		B ·5 mm. Pt. + 2·0 mm. Paraffin.		C 1·0 mm. Pt. + 1·5 mm. Paraffin.		D 1·5 mm. Pt. + 1·0 mm. Paraffin		E 2·0 mm. Pt. + ·5 mm. Paraffin.		F 2·0 mm. Pt.	
	Mitoses.	Plasma Cells.		Mitoses.	Plasma Cells.	Mitoses.	Plasma Cells.	Mitoses.	Plasma Cells.	Mitoses.	Plasma Cells.	Mitoses.	Plasma Cells.	Mitoses.	Plasma Cells.
High Columnar Region.	3·6	24·4	3	5·7	34·0	6·5	54·6	21·0	15·7	11·2	30·0	17·7	26·3	8·8	37·3
			6	13·8	40·2	4·3	24·8	8·5	36·5	14·3	19·8	8·2	28·9	10·5	26·3
			9	28·4	76·8	9·6	46·1	6·3	43·7	9·2	36·1	11·5	61·0	8.3	22·9
			Means -	16·0	50·3	6·8	41·8	11·9	32·0	11·6	29·3	12·5	38·7	9·2	28·2
Low Columnar Region.	9·9	18·0	3	2·8	24·6	7·8	16·0	17·6	14·0	12·4	12·1	12·6	12·6	14·4	23·0
			6	9·2	26·4	14·3	23·6	9·3	28·5	5·1	14·0	13·6	22·6	6·9	22·9
			9	26·7	63·2	4·6	30·7	4·3	36·9	18·6	35·1	3·8	20·7	3·6	19·6
			Means -	12·9	38·1	8·9	23·4	10·4	26·5	12·0	20·4	10·0	18·6	8·3	21·8
Moist Squamous Region.	1·16		3	1·6		0·68		2·56	—	1·08		0·76		0·64	
			6	1·52		0·08	—	0·8	—	1·4	—	0·68	—	0·36	—
			9	3·52		1·08	—	1·16	—	0·88	—	0·8	—	0·28	—
			Means -	2·21		0·61		1·51		1·12		1·41		0·42	
Dry Squamous Region.	2·26		3	0·6		0·98		1·08	—	2·12		0·98		0·48	
			6	0·92		1·88		1·14		2·56		1·3		0·96	
			9	1·1		0·72		0·76		0·48		0·52		0·36	
			Means -	0·97		1·13		0·99		1·72	—	0·93		0·6	—

Examination of the values of mitoses in Table II. indicates a tendency for the minimum number of mitoses to be found on a later day when the platinum screen is thick than when it is thin. Thus, with two exceptions, the minimum number of mitoses in Series A and B was found in the third or sixth day specimen, whereas in series E and F the minimum number of mitoses (with one exception) was found in the sixth or ninth day specimen.

Summary.

We are now in a position to sum up the various data and attempt to arrive at a conclusion as to the effect of screening radium when it is used for clinical purposes.

In treating a neoplasm with radium the ideal is clearly to damage the reproductive activity of the neoplastic cells to as great an extent as possible while the minimum damage is done to the non-malignant tissues. Figures have been given in Table I., by means of which a rough estimate can be made of the general damage to the tissues. Taking the number of plasma cells as a rough indication of the degree of inflammation of the tissues, one is able to say that *undesirable* damage varies directly as the number of plasma cells. Similarly the number of mitotic cells is an indication of *desirable* damage which varies inversely as the number of mitotic figures present. If then the normal number of plasma cells or mitotic figures be taken as 100, a simple calculation will give an idea as to the extent to which the desired object has been attained. Thus taking the observed values for the experiment of the third day in Series A (Table II.), it is seen that the mitoses in the high columnar region are $\frac{5 \cdot 7}{3 \cdot 6}$ normal. Similarly in the low columnar region the mitoses are $\frac{2 \cdot 8}{9 \cdot 9}$ normal. Since our desire is to reduce mitoses in radium treatment of new growths, the $\frac{2 \cdot 8}{9 \cdot 9}$ is favourable, for we have reduced the proliferative activity to about a quarter; the $\frac{5 \cdot 7}{3 \cdot 6}$ is unfavourable, because actual stimulation has occurred. In considering the relative values of different methods of applying radium it is necessary to appraise the degree of

Table III.

Table to show the effect of radium upon the epithelium and sub-epithelial tissues of the rat's rectum and tail, according to the degree of screening. Values have been given to the various components according as they are unfavourable (below 100) *or favourable (above* 100 *to the objects of* (a) *minimum damage to the tissues and* (b) *maximum damage to proliferative activity. Normality in all instances* = 100.

Region.	Component.	A Screen 0·5 mm. Pt.	B Screen 0·5 mm. Pt. +2·0 mm. Paraffin.	C Screen 1·0 mm. Pt. + 1·5 mm. Paraffin.	D Screen 1·5 mm. Pt. + 1·0 mm. Paraffin.	E Screen 2·0 mm. Pt. + 0·5 mm. Paraffin.	F Screen — 2·0 mm. Pt.
High Columnar.	Gen. conditions	67	70	78	74	75	86
	Plasma cells ...	48	58	76	83	63	85
	Mitoses... ...	23	53	30	31	29	39
	Total	138	181	184	188	167	210
Low Columnar.	Gen. conditions	66	55	74	78	86	80
	Plasma cells ...	47	77	68	88	97	83
	Mitoses... ...	77	111	95	83	99	119
	Total	190	243	237	249	282	282
Moist Squamous.	Gen. conditions	65	69	83	79	85	73
	Plasma cells ...		—	—		—	—
	Mitoses... ...	52	190	77	104	82	276
	Total	117	259	160	183	167	349
Dry Squamous.	Gen. conditions	59	56	52	72	69	79
	Plasma cells ...	—	—	—	—	—	—
	Mitoses... ...	233	200	228	131	243	377
	Total	292	256	280	203	312	456

advantage or disadvantage, and this can be done by means of the formula

$$\frac{\text{normal number of mitoses (or plasma cells)}}{\text{observed number of mitoses (or plasma cells)}} \times 100.$$

where 100 is arbitrarily taken to indicate normality.

This has been done for the mean values in Table II., and in Table III. they are presented along with the values ascribed to the general conditions (Table I.).

In spite of irregularities it may be said that the ideal in treatment of minimum damage to normal tissues and maximum damage to proliferate activity of the epithelial cells is approached the more heavily the radium is screened with platinum. Thus comparing Series A (·5 mm. Pt.) with Series F (2 mm. Pt.) it is seen that more satisfactory results are obtained with the heavy screening, not only in situations actually touching the radium tube, but also in regions at a short distance.

The same conclusion in favour of heavy screening is produced if we combine the various totals for Series A, B, C, and compare them with the correspondingly summed totals for Series D, E, F.

	Series A, B, C.	Series D, E, F.
High Columnar	503 ...	565
Low Columnar	670 ...	813
Moist Squamous	536 ...	699
Dry Squamous	828 ...	971

If we consider the high and low columnar regions alone as being those from which the most satisfactory data can be obtained the grand totals—

Series ...	A	B	C	D	E	F
Grand total ...	328	424	421	437	449	492

clearly indicate that the advantage lies with an increasing thickness of the platinum screen.

Whether the anomalous position of Series B (in which the radium tube itself was simply surrounded by 2 mm. of paraffin) is real or accidental is uncertain. Undoubtedly this arrangement was associated with a pronounced effect upon mitosis, but more experiments would be needed before a screen of paraffin could be contrasted with a screen of platinum.

The present experiments, however, strongly suggest that, *provided the ionisation value be kept constant*, both from the point of view of reducing proliferative activity of the epithelial cells to a maximum and from that of injuring normal tissues to a minimum, the efficacy of radium treatment of malignant disease would vary directly with the thickness of the platinum with which the radium is screened.

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